THE SURGICAL CLINICS OF NORTH AMERICA

OCTOBER 1970

RESPONSE TO INFECTION AND INJURY II

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THE SURGICAL CLINICS OF NORTH AMERICA

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SYMPOSIUM ON
RESPONSE TO INFECTION AND INJURY
II. Metabolism

George H. A. Clowes, Jr., M.D., *Guest Editor*

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GEORGE H. A. CLOWES, JR.

Foreword

Survival or death depends upon the dynamic balance between the magnitude of the injury inflicted by trauma or sepsis and the adequacy of the protective physiologic responses essential to preserve the supply of substrates and the milieu required for cellular metabolism and function throughout the body. In addition to the local impairment of function caused by trauma and the accompanying infection, far-reaching damage to cells in distant parts of the body may occur. Malfunction of any organ can interfere with the metabolism and function of others. At the same time toxic agents emanating from the site of injury or sepsis may be responsible for a variety of serious consequences. These changes range from clotting abnormalities to alterations in energy metabolism and protein synthesis.

The purpose of this symposium is to define the nature of the injurious processes commonly encountered in surgery and the pattern of responses which preserve life until the focus of trauma or sepsis is contained and ultimately resolved. Understanding of the factors contributing to the total injury and stress to which a patient may be subjected makes apparent methods for eliminating them or reducing them to a minimum. This concept is true not only in the operating room, where presumably the correct procedure is carried out, but also in the preoperative and postoperative periods. By the same token, knowledge of the normal pattern of recovery permits recognition clinically of serious deviations or the failure of any vital system. Thus, effective preventive or supportive therapy can be instituted.

Finally, abnormalities of energy metabolism leading to proteolysis can seriously impair protein synthesis upon which depend wound healing and immunocompetence against bacterial invasion. All emphasize the importance of early and aggressive nutritional support for prevention of such sequelae.

This undertaking has resulted in the collection of a series of authoritative articles by a distinguished group of authors. To each one go our thanks for willingness to put in writing the various aspects of the physi-

ology and metabolism which pertain to survival and recovery of the surgical patient. Because of the magnitude of this subject, this symposium appears in two consecutive issues of *Surgical Clinics of North America*. The first deals principally with physiology, and the second with metabolism. Also, appreciation must be expressed for the fine cooperation of Mr. Paul Dolgert and other members of the editorial staff of the publishers.

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Hormonal Responses and Their Effect on Metabolism

*Douglas W. Wilmore, M.D.**

The name "hormone," derived from the Greek root "hormaein" (meaning to excite, arouse, or set in motion), was proposed by Starling to describe chemical agents which are released from one group of cells, travel by the blood stream, and affect other cell populations. Huxley placed less emphasis on the mode of travel of these substances and suggested that the prime role of hormones is to *transfer information* from one set of cells to another, to evoke a response beneficial for the cell population as a whole. The body's response to stress, described as the "flight or fright mechanism," the "alarm reaction," the "general adaptation syndrome," or simply body homeostasis, characterizes these hormonally mediated adjustments which are essential for survival.

Recent advances in hormonal assay, particularly with the development of immunoassay techniques for quantification of small peptide molecules, allows changes in the level of specific "information transfer units"—hormones—to be related to specific stimuli, evoked by alterations in the external environment or the internal milieu. Additional studies designed to evaluate the effect of hormonal administration or hormone blockade have further characterized the biochemical and physiologic alterations which are "set in motion" by hormonal mediators. This article reviews the endocrine response to major stress and relates these hormonal changes to the alterations in physiology and biochemistry of critically ill surgical patients.

THE HORMONES

Catecholamines—The Hormones of Stress

Shortly before the turn of this century, an aqueous extract was obtained from the adrenal medulla which produced a prompt rise in blood pressure. Six years later, the active principal was isolated and called adrenalin, epinephrine, adrenin, or suprarenin. Since then, many inter-

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mediate steps in the synthesis of epinephrine and norepinephrine have been determined and the storage, release, and transmission of these neurotransmitters described[26] (Fig. 1). Studies by Von Euler are clinically significant, for he found norepinephrine in the postsynaptic sympathetic ganglion and developed assay techniques which related catecholamine blood levels or excretion rates to a wide variety of stress states.[37]

Walter B. Cannon and his colleagues provided convincing evidence that the catecholamines were liberated during stress and were, in fact, essential for maintaining body homeostasis following a wide variety of stressful stimuli.[7] Utilizing the rate of denervated heart as a biological indicator of adrenal medullary catecholamine release, Cannon found heart rate increased with fright, rage, pain, asphyxia, anesthesia, muscular activity, cold exposure, and sensory nerve stimulation. Removal or denervation of the adrenal glands, or ligation of the adrenal veins, abolished this response. He then removed all the sympathetic ganglia from cats: the animals remained in good health, living long lives and even reproducing as long as they were maintained in the warm, sheltered environment of the laboratory. However, the sympathectomized animals were particularly vulnerable to stress, unable to defend against hypoxia, fluid restriction, variations in environmental temperature, or hemorrhage, or to adapt to a variety of other external or internal stresses. The sympathetic nervous system, transmitting signals by way of the catecholamines, was *essential for survival during stress.*

The dramatic effect of sudden sympathoadrenal discharge is observed in an injured animal. The "flight or fright" response is characterized by tachycardia, pupillary dilation, piloerector activity of the skin, alterations in skin and muscle blood flow, and an increased respiratory rate associated with bronchial dilatation. This physiologic response is accompanied by an outpouring of glucose and free fatty acids into the blood stream and release of hormones which signal for salt and water retention. Cuthbertson has emphasized that at the time of injury there may be a depression in the physiologic response to the hormonal discharge

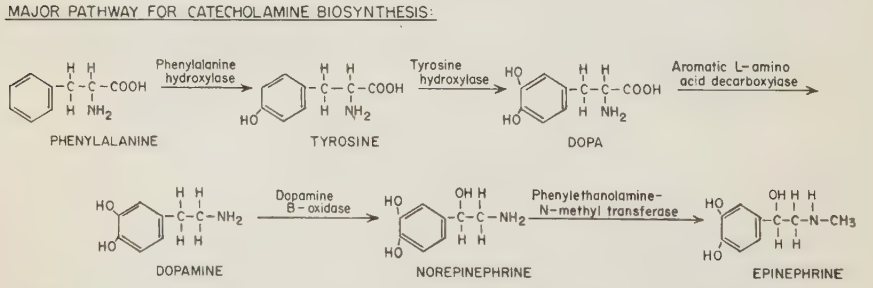

Figure 1. Phenylalanine cannot be synthesized by the body and, hence, is an essential amino acid. Enzymatic conversion to tyrosine occurs in the liver by a complex hydroxylation system, which is absent in children with phenylketonuria and may be rate-limiting in patients with liver disease or premature babies with immature liver function. Tyrosine is transported from the blood stream to various sites of catecholamine synthesis. The rate-limiting step for catecholamine synthesis appears to be tyrosine hydroxylase, which is influenced by dietary tyrosine and the quantity of catecholamine released. With the appearance of the catechol end product, there is an increased rate of hydroxylation of tyrosine. The enzyme for conversion of epinephrine to norepinephrine is found in high concentrations in the adrenal medulla.

("ebb phase"), which may be transitory and a manifestation of circulatory inadequacy or neurogenic shock.[8] If the organism survives the initial injury, the early response is generally followed by an increase in metabolic reactions ("flow phase"), presumably to provide substrate for the inflammatory response and tissue repair. The metabolic responses described in this review are characteristic of the "flow phase" of injury.

Catecholamines elicit a variety of physiologic effects: specific tissues may in fact respond in an opposite manner when the effect of epinephrine is compared to the norepinephrine response. In addition, a low dose of this neurohormone may elicit an entirely different response than a high dose of catecholamine. These paradoxical effects are attributed to the presence of a dual receptor system present in most tissues. Utilizing pharmacologic blocking agents, a specific effect can be attenuated by competitive receptor blockade and the observed response attributed to alpha or beta adrenergic receptor stimulation, depending upon the blocking agent utilized. Epinephrine and norepinephrine stimulate both receptor systems, but epinephrine exerts predominantly beta effects and norepinephrine exhibits predominantly alpha characteristics. With the discovery of cyclic AMP, the second or "intracellular" messenger, the adrenergic beta receptor system has been proposed as an integral part of the adenyl cyclase system.[30] Beta receptor stimulation causes an increase in the intracellular level of cyclic AMP. Conversely, alpha receptor effects may be mediated by a fall in the intracellular concentrations of cyclic AMP.

Catecholamines affect circulation, cardiac function, and respiration, but only the specific metabolic effects will be considered in this discussion. Hyperglycemia occurs following the injection of epinephrine as a response to a complex series of interactions. First, there is a direct effect on the liver, increasing the conversion rate of glycogen to glucose and simultaneously directing conversion of three-carbon precursors to glucose. Second, epinephrine acts directly on skeletal muscle, converting skeletal muscle glycogen to lactic acid, which is transported to the liver and converted to new glucose (Cori cycle). Beta receptors characteristically mediate this effect. Finally, epinephrine has a direct effect of the pancreas, suppressing the release of insulin which would normally occur with an elevated blood glucose level.[21, 28] Simultaneously, pancreatic glucagon is stimulated.

The calorigenic effects of catecholamines may represent one of the most important effects of these hormones. Catecholamines infused into animals increase metabolic rate and epinephrine or norepinephrine infusions in normal man produce hypermetabolism.[33, 39] Rats in which adrenergic function is completely blocked die in 3 hours when exposed to 4°C ambient environment, while normal animals adjust to the temperature by increasing their metabolic rate.[11] These effects are blocked by beta adrenergic receptor antagonists and not affected by alpha blockade.

Mobilization of free fatty acids occurs following sympathetic stimulation, a result of the direct action of catecholamines on fat cells. The lipolytic effect of catechols is potentiated by suppression of insulin release from the pancreatic beta cell; low insulin levels favor fat mobilization, while high insulin concentrations augment fat storage. Catecholamines exert a variety of effects on muscle, in addition to positive chronotropic and

ionotropic effects on the heart. Catecholamines facilitate neuromuscular transmission and increase repetitive firing and twitch response of skeletal muscle following stimulation.[30] This effect is attributed to the ability of catecholamines to increase release of acetylcholine from nerve endings. The muscle tremors and reflex hyperactivity frequently observed in critically ill patients are believed to be a clinical manifestation of this effect.

Insulin—The Storage Hormone

Insulin promotes the storage of metabolic fuels within cells. This storage effect is augmented by several other hormones and the parasympathetic nervous system, but insulin plays the dominant role in converting body substrate to storage fuels (Fig. 2). In the nonstress state, insulin responds to blood glucose concentrations to facilitate glucose entry into many tissues. Insulin is essential to glucose homeostasis: pancreatectomized man must receive insulin to survive.[6] In the liver and skeletal muscle, insulin promotes the synthesis of glycogen, the storage form of glucose. Lipogenesis decreases in insulin-deprived man, and, in the presence of lipolytic stimuli (such as catecholamines), the rate of triglyceride breakdown is greatly accelerated when insulin concentrations are low. The mobilized free fatty acids may be converted to water soluble "ketone bodies" in the liver, and, in the absence of insulin or in the glucose-deprived state, the rate of ketone production may exceed peripheral uptake, resulting in "ketosis." When insulin is low or absent, plasma amino acid concentrations rise. Insulinization of the skeletal muscle will reverse this effect by augmenting the transport of amino acids into the muscle cell and limiting amino acid efflux from the protein stores.[4] Amino acid transport appears to be independent of the enhanced intracellular protein synthesis which is stimulated by insulin. Finally, insulin facilitates transport of potassium and phosphorus into the cell, ionic movement which occurs simultaneously with the intracellular flux of glucose.

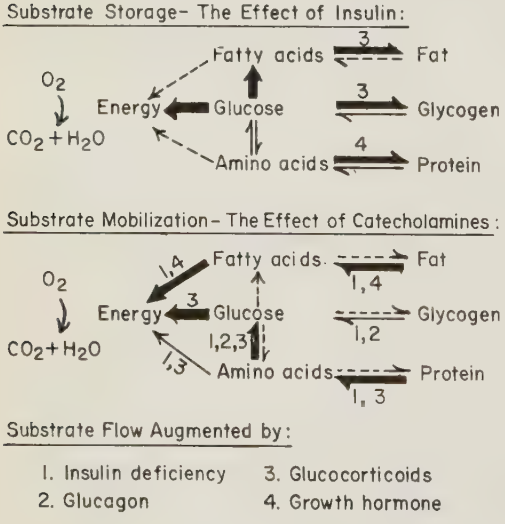

Figure 2. Hormonal effects on storage and mobilization of body fuels.

The interaction between the autonomic nervous system and the endocrine pancreas is fundamental to the regulation of substrate storage or mobilization following stress.[29] Catecholamines suppress insulin release,[28] and the increased sympathetic nervous system activity appears to be responsible for the insulin suppression and glucose intolerance observed during operation, hemorrhagic shock, mild or severe infection, and burn shock. The insulin inhibitory effect of the sympathetic nervous system is mediated by alpha receptors, while adrenergic beta receptor stimulation augments insulin elaboration (Fig. 3).[20] During the early or ebb phase of injury, alpha receptor effects appear to dominate, resulting in glucose intolerance. The flow phase is characterized by increased heat production (a beta adrenergic effect) and increased mass flow of glucose from the liver to the peripheral tissue is related to the hypermetabolism which occurs.[45] Beta adrenergic receptors may augment insulin elaboration during this flow phase of injury. Other feedback mechanisms aid in the maintenance of glucose homeostasis following stress. For example, insulin is suppressed by lactic acid and insulin is stimulated by high levels of glucagon. All these control mechanisms may be over-ridden by alterations in blood flow to the endocrine pancreas, which could occur during hypovolemia, cardiac failure, or with alterations in blood flow directed by increased autonomic nervous system discharge.

Glucocorticoids, Glucagon, Growth Hormone—The Permissive Hormones

ACTH release follows a wide variety of stress and elicits an outpouring of glucocorticoids from the adrenal cortex. Adrenalectomized animals maintained on a constant dose of glucocorticoids respond to injury in the expected manner.[18] Thus, the effect of glucocorticoids was defined as permissive, augmenting or amplifying specific metabolic responses to stress. Glucocorticoids administered to fasting man do not increase nitrogen excretion,[27] and the protein wasting associated with systemic infection is not attributable to the effects of endogenous corticosteroids.[3]

Glucocorticoids provide specific signals for augmenting hepatic gluconeogenesis by stimulating enzymes which direct conversion of three-carbon fragments into synthesis of new glucose. Increased

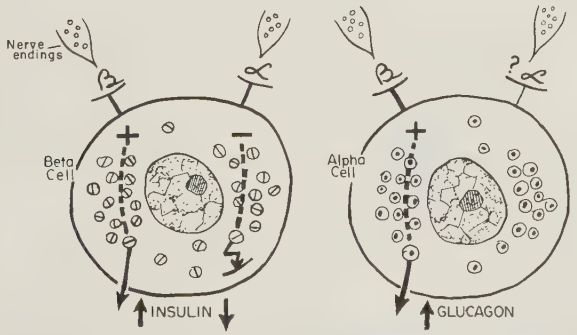

Figure 3. Insulin and glucagon releases are stimulated by beta adrenergic receptors, and insulin release is inhibited by alpha receptor stimulation. The presence of an alpha inhibitory effect on glucagon is thought not to occur.

gluconeogenesis occurs in animals when glucocorticoids are administered in conjunction with catecholamines.[19] This effect occurs primarily in the liver, but increased mobilization of amino acids from the periphery may be stimulated by glucocorticoids, although this effect in injured man is yet to be confirmed. Finally, glucocorticoids augment lipolysis and catecholamine stimulated glycogen oxidation in skeletal muscles.

Glucagon has potent hepatic glycolytic and gluconeogenic activities, hormonal properties precisely opposite those of insulin. The interaction between insulin and glucagon has been proposed as the determinant of hepatic glucose balance in fed and fasting man and diabetic patients.[35] Anabolism and protein conservation occurs when insulin is increased relative to glucagon, a hormonal environment which favors energy storage, limits gluconeogenesis, increases protein biosynthesis, and decreases urea nitrogen excretion. Starvation in normal man, diabetes, or infusion of glucagon into fasting man, increases glucagon relative to insulin, and this hormonal milieu is associated with increased glycogenolysis, gluconeogenesis, and ureagenesis at the expense of protein biosynthesis.[24]

In traumatized[38] or infected patients,[31] glucagon levels are elevated even in the face of glucose administration and hyperglycemia. Glucagon elaboration is stimulated by hypoglycemia, increased sympathetic activity, and certain amino acids. The close relationship between glucagon and catecholamines in severely injured patients suggests that increased adrenergic activity may mediate the post-traumatic hyperglucagonemia occurring after injury. The return of glucagon to normal coincides with healing of the wound when urine catecholamines fall to normal levels. Therefore, catecholamines appear to direct the pancreatic islet cell elaboration of both insulin and glucagon—that is, to adjust setpoints for the hormonal responses of the endocrine pancreas—and these hormones, in turn, control the disposition of key substrates. Glucagon exerts its effect primarily on the liver, augmenting catecholamine directed, cyclic AMP mediated, hepatic gluconeogenesis. Glucagon does not contribute to the efflux of amino acids from skeletal muscle.[12]

Growth hormone is stimulated during stress and resets the insulin response to glucose, stimulates free fatty acid release favoring fat utilization in the periphery, and augments nitrogen retention in fed man. Increased nitrogen retention does not occur when HGH is administered to fasting man.[25] However, HGH administered to critically injured patients with sufficient nutrients to maintain energy balance improves nitrogen retention during the catabolic stage of injury.[40] These effects appear to be mediated by alterations in carbohydrate metabolism in the presence of augmented insulin production.

HORMONAL EFFECTS ON METABOLISM

Hypermetabolism

Increased basal metabolic rates occur with thyrotoxicosis, peritonitis, soft tissue or systemic infection, major trauma, and thermal injury. The increase in metabolism is related to the severity of injury or infection.

Following thermal injury, metabolic rate increases in a linear manner in patients with up to 40 to 50 per cent total body surface burn, and then plateaus, suggesting that patients with larger surface area burns respond in a similar manner by attaining maximal or near maximal levels of heat production. Metabolic rate rarely exceeds twice normal levels in hospitalized diseased-stressed patients, and this should be considered as the upper limit for heat production in critically ill patients supine in bed. Metabolic rate also varies with time postinjury, and oxygen consumption which may be near normal during resuscitation rises and peaks during the flow phase of injury and decreases in a curvilinear manner to return to predicted basal levels when wound healing or resolution of the infection is achieved (Fig. 4).

The etiology of the hypermetabolic response following injury has been studied extensively, but the precise mechanism has been defined only recently. Studies in thermally injured patients with the most prodigious increases in metabolic rate observed following injury allow characterization of the time response, central nervous system drives, and hormonal mediators of the response to this stress. Increased water loss from the burn wound results in surface cooling and may stimulate metabolic heat production in order to generate more heat and maintain body temperature. Since increased oxygen consumption and insensible water loss are both correlated with burn size, hypermetabolism has previously been related to surface cooling secondary to increased evaporative water loss

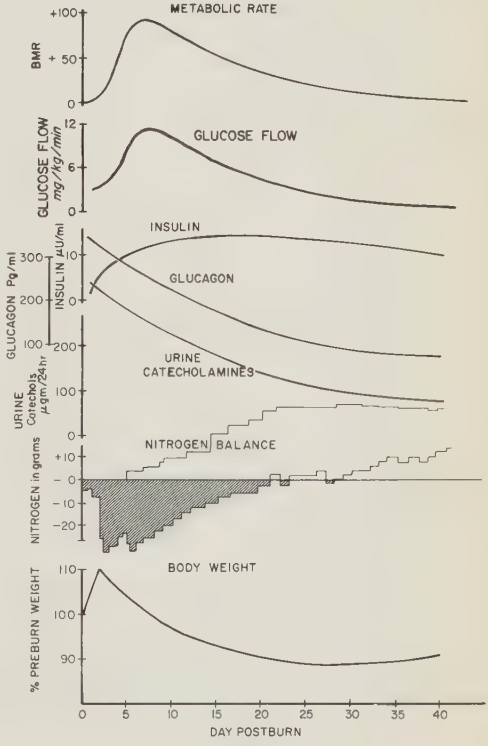

Figure 4. The sequence of metabolic events which occurs following thermal injury is related to hormonal control. Note that glucose flow parallels oxygen consumption, is elevated during periods of negative nitrogen balance, and returns to normal levels when weight stabilization and nitrogen equilibrium are achieved. Increases of catecholamine and glucagon relative to insulin appear to mediate this response. (Figs. 4, 5, and 6*B* reproduced from Wilmore, D. W.: Nutrition and metabolism following thermal injury. CLIN. PLAST. SURG., *1*:603–618, 1974.)

from the burn wound.[2] Thermally injured patients treated in a warm environment (32°C) decrease metabolic rate, compared with treatment at 22°C,[2] and this evidence has been interpreted to support the thesis that hypermetabolism in burn patients is a response to increased surface cooling due to increased evaporative water loss. However, Zawacki and associates covered the burn wound with a water-impermeable membrane (blocking evaporative water loss) but found no consistent alteration in metabolic rate in burn patients studied at approximately 25°C ambient temperature.[46]

Studies of burn patients in the rigidly controlled ambient conditions of an environmental chamber demonstrate a curvilinear relationship between metabolism and burn size, but a direct linear relationship between evaporative water loss and per cent total body surface burn.[41] In the normal subjects studied, and in patients with burns of less than 40 per cent total body surface, metabolism (at 25°C and 50 per cent relative humidity) was not related to surface cooling by evaporative water loss. Hence, metabolic rate was unaffected when these individuals were studied at a warmer ambient temperature (Fig. 5). However, as metabolic rate plateaus in patients with burns of greater than 40 per cent total body surface, evaporative water loss increases in a linear manner, contributing to a disproportionate increase in heat transfer by vaporizational heat loss, resulting in the slight increase in metabolic rate at 25°C when compared with 33°C. The patient's response to the cooler temperature is characterized by an inability to vasoconstrict, insulate the body, and diminish or limit heat transfer from the body's core to the surface.[41]

These studies demonstrate that evaporative water loss in the burn patient is not the prime stimulator of the hypermetabolic response, but rather the increased energy production is related to an endogenous reset in metabolic activity. This basic metabolic drive is then influenced by environmental conditions. At any ambient temperature measured, the

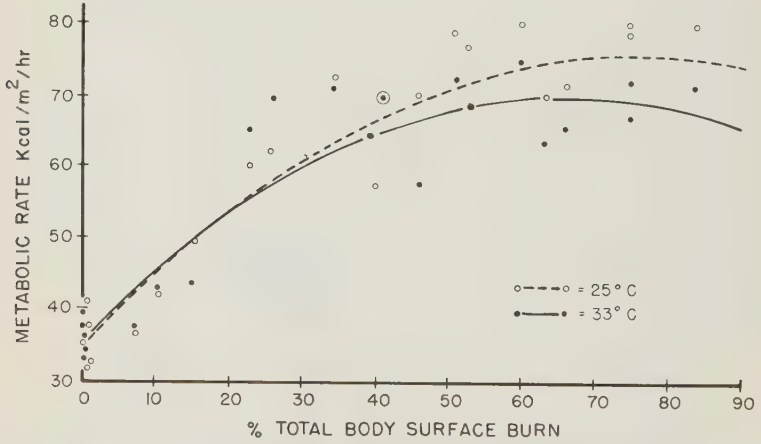

Figure 5. Burn patients are internally warm, not externally cold, and do not reduce their metabolic rates to normal when placed in a warm environment.

core and mean skin temperature of the burn patient is well above temperatures measured in normal man.[39] The injured patients are internally warm, not externally cold, and this internal reset in the production of heat is characterized by the post-traumatic hyperpyrexia which occurs following injury. Metabolic rate does not return to normal levels with treatment of burn or fracture patients in a warm environment.

Catecholamines are elevated following thermal injury, and adrenergic activity has been related to the extent of burn and to the oxygen consumption of the patient. Carefully controlled adrenergic blockade in patients with large surface area burns demonstrated a consistent decrease in metabolic rate with alpha and beta or beta adrenergic blockade alone.[39] Administration of epinephrine and norepinephrine to normal man increases metabolic activity. This evidence suggests that increased catecholamines (increased adrenergic activity) are the major calorigenic mediators responsible for the hypermetabolic response following injury. Increased calorigenesis has also been noted with growth hormone administration and infusion of glucagon.[1] The physiologic significance of these effects is yet to be determined, but these hormonal mediators may augment or potentiate the catecholamine directed heat production which occurs in injured man.

The ability to respond to a stimulus requiring catecholamine calorigenesis depends upon the availability of catecholamine reserves and the ability of tissues to respond to increased catechol stimuli. Reports evaluating catecholamine stores in patients who die following injury and stress demonstrate depletion of these neurotransmitter reserves in adrenal medulla, sympathetic nerve endings and sympathetic ganglia,[13] and heart.[22] Dopamine turnover in burn patients is markedly increased[14] and serum tyrosine concentrations are low, possibly reflecting substrate limitation.[14] Burn patients with injuries of more than 40 per cent of the body surface appear to maintain maximal or near maximal rates of catecholamine synthesis and utilization. Exposing these patients to a cool environment (21°C) results in a mild cold stress, ordinarily a stimulus for the elaboration of additional catecholamines. Patients who eventually survived responded by increasing heat production as a result of greater elaboration of catecholamines. In contrast, patients who lacked catecholamine reserves or tissue responsiveness to these mediators failed to generate sufficient additional heat to maintain heat balance in the 21°C ambient temperature and became hypothermic (Fig. 6). All of the nonresponding patients subsequently died from complications of their injury. Like Cannon's sympathectomized cats, the nonresponders lacked homeostatic reserve, for injury had reset their rates of energy production at a maximal level. Additional sympathetic nervous system reserves were unavailable for catecholamine mediated responses to cooling, infection, and hemorrhage.

What directs the release of catecholamines from the sympathetic nervous system and adrenal medulla? The sympathetic center in the brain is located in the hypothalamus and is intimately related to the thermoregulatory areas, the satiety center, and control mechanisms for maintenance of glucose homeostasis. The afferent signals to the brain

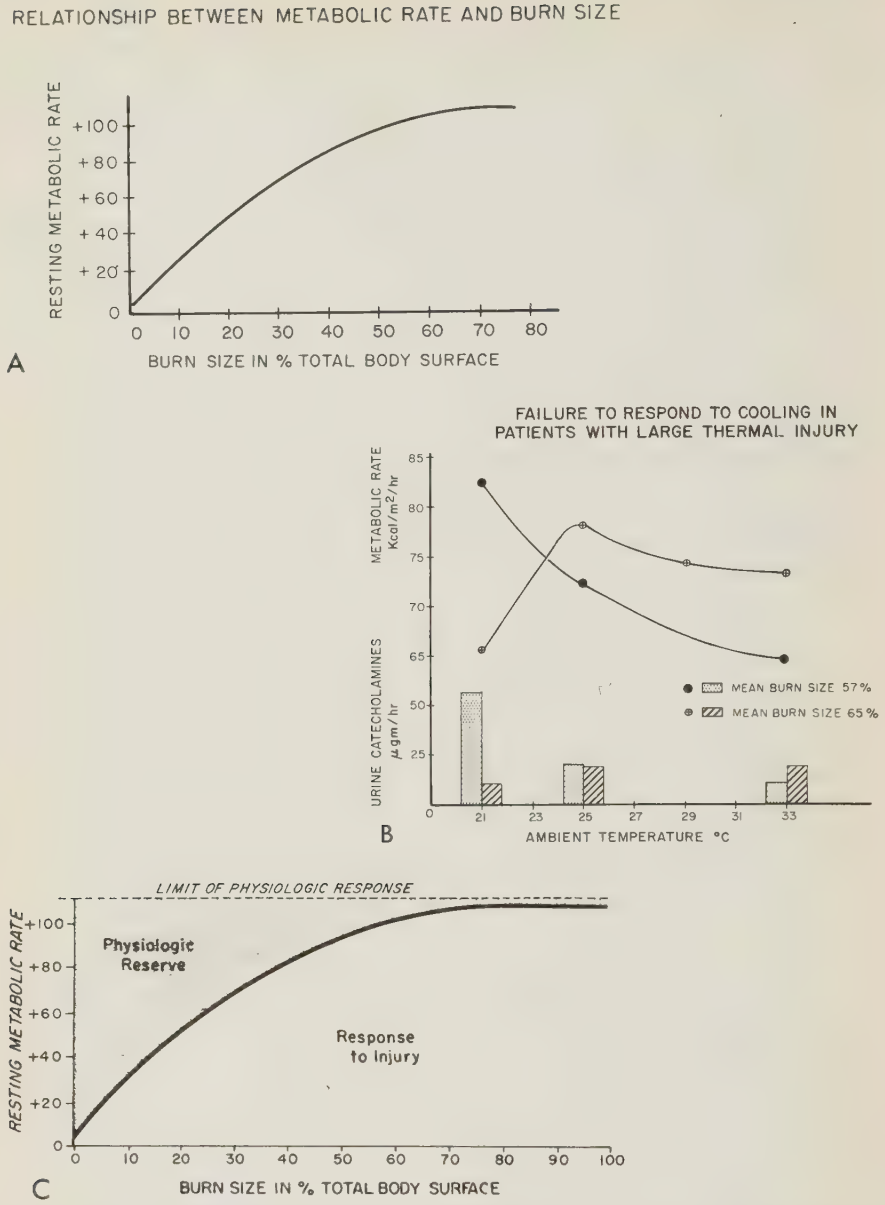

Figure 6. *A*, Metabolic rate increases linearly with burn size, then plateaus in patients with massive thermal injury, suggesting that these patients are at maximal or near maximal rates of heat production. This thesis is tested by studying the response of patients with extensive burn injuries in a cool environment. *B*, Some patients are able to respond by increasing catecholamines and heat production, but others with inadequate sympathetic reserve or lack of tissue responsiveness to catecholamines failed to generate additional heat and became hypothalamic. This difference is essentially burn-size related. *C*, These data suggest that patients with extensive injury lack "physiologic reserve" because they have achieved maximal or near maximal rates of heat production and other physiologic stress responses and cannot generate further homeostatic adjustment to respond to complications of infection, hemorrhage, or environmental stress.

following infection are well known: either exogenous pyrogen from bacteria cell walls ("endotoxin") or endogenous pyrogen liberated from our own phagocytic cells provides the biochemical pyrogen which is carried by the blood stream to the thermoregulatory area. These chemical substances then cause a reset in central temperature "setpoint," resulting in adjustments in the body's mechanisms for heat production and heat conservation. During fever, the temperature controller in the brain calls for an elevated temperature and, acting through the nervous system, evokes stimuli which achieve this warmer temperature through vasoconstriction and hypermetabolism. With resolution of the infection, the "setpoint" returns to normal, heat is lost from the body, and core and tissue temperatures return to normal levels.

The mechanisms for stimulation of the sympathetic center following trauma or burn injury are not as well understood. The quickest route for signalling the brain that tissue injury has occurred is by sensory nerves, and the importance of the afferent nervous signals to the hypothalamus has well been described following pain, hypoxia, hypotension, or hypovolemia.[44] In addition, afferent nervous signals are essential for the immediate release of ACTH and ADH following stress. In the flow phase of injury, denervation of the wound or interruption of the sensory input to the brain does not appear to diminish the hypermetabolic response to thermal injury (Table 1).

An apparent reset in central temperature regulation occurs in the thermally injured patient. At any ambient temperature studied, burn patients demonstrate an elevated core and skin temperature when com-

Table 1. *The Effect of CNS Injury and Afferent Nervous Blockade on Post-Traumatic Hypermetabolism (Mean, Range, or ± S.E.)*

CNS INJURY	N	BURN SIZE (PER CENT BSA*)	AGE (YEARS)	POSTBURN DAY STUDIED	METABOLIC RATE (KCAL PER M^2 PER HR) Measured	Predicted From Burn Size
Cerebral contusion	1	26	15	15	65.6	53.0
Cerebral contusion	1	48	23	8	88.2	68.0
Cerebral contusion (T-11 spinal cord transection)	1	60†	27	3	92.0	74.4
Cerebral edema (flat EEG)	1	23	19	3	30.8	56.1
Afferent Nervous Blockade					Before	After
Topical anesthesia to burn wound	3	66 (53–78.5)	28 (25–30)	13 (10–17)	77.8 ± 4.2	77.5 ± 2.5
Spinal anesthesia	1	33‡	39	33	57.3	63.8

*BSA = body surface area.
†Burn over lower trunk and lower extremities.
‡Multiple fractures and burns of lower extremities.

pared with normal man. When burn patients and normals were allowed to regulate the ambient temperature to achieve comfort, the mean ambient temperature selected for comfort by the patients was significantly increased when compared to normal man.[43] The ambient temperature selected was related to the size of injury. During comfort, the burn patients had a significantly higher core and mean skin temperature than the normal individual. Reset or readjustment in hypothalamic temperature setpoint following injury is suggested by the fact that burn patients felt comfortable at elevated ambient temperatures which were uncomfortable for normal man. The maintenance of elevated body temperatures during comfort is similar to the response to central temperature readjustment which occurs during the febrile response to infection.

The central temperature readjustment in injured man appears refractory to the usual pharmacologic manipulation, and only central nervous system narcosis[34] has decreased sympathetic stimulation resulting in a fall in metabolic rate (Table 2). Currently, we are treating patients at temperatures of comfort (28–33°C), and this ambient environment maintains elevated core temperatures (38–39°C). The patients are constantly surveyed for infection, which is often demonstrated initially by marked deviation from an otherwise rather stable elevated core temperature and appearance of glucosuria. While maintaining these individuals in the febrile-uninfected state, they receive vigorous nutritional support to minimize breakdown of body mass ("feed a fever").

Negative Nitrogen Balance and Loss of Other Intracellular Constituents

In the early 1900's, increased loss of body protein was described in patients with infectious diseases, and, during World War I, acceleration of protein catabolism was described as a metabolic consequence of injury. Yet it was not until Cuthbertson and associates demonstrated the increased loss of nitrogen and other intracellular constituents following long bone fracture that alterations in protein economy became a recognized feature of the post-traumatic metabolic response to injury.[8] Following moderate to severe trauma in otherwise healthy adults, there is a marked rise in urinary nitrogen, sulfur, phosphorus, potassium, magnesium, zinc, and creatinine. The rise in urinary nitrogen is primarily an increase in urea, which comprises approximately 85 to 90 per cent of the total urinary nitrogen. Abnormal protein loss from the gastrointestinal tract does not occur, and most patients with previously normal intestinal function, receiving hospital diets, lose less than 2 gm of nitrogen per day in their stools unless diarrhea is present. However, protein loss from an open wound is significant, and burn wound loss contributes approximately 20 to 25 per cent of the total nitrogen lost from the body in the early postburn period, with surface losses decreasing in time and returning to normal with closure of the burn wound. Wound loss represents only a fraction of the total nitrogen lost from the body, and the mechanism of protein leak through the wound is distinctly different from the hypercatabolic process. This process, mobilizing amino acids from body protein stores, converts the carbon fragments in the liver to new glucose (gluconeogenesis), and handles the nitrogen residue by forming urea (ureagenesis), which is excreted in increased quantities in the urine.

Table 2. *Administration of Agents Thought to Interact with Central Temperature Regulation (Mean, Range, or ± S.E.)*

TREATMENT	N	BURN SIZE (PER CENT BSA*)	AGE (YEARS)	POSTBURN DAY STUDIED	METABOLIC RATE (KCAL PER M^2 PER HR)		CORE TEMPERATURE (°C)	
					Before	After	Before	After
Aspirin	3	52 (41–57)	18 (14–22)	29 (13–39)	70.4 ± 7.6	71.2 ± 5.9†	38.1 ± 0.3	38.2 ± 0.4
L-Dopa	7	46 (36–51.5)	28 (24–36)	16 (7–25)	54.8 ± 5.7	57.0 ± 5.9	37.5 ± 0.5	37.4 ± 0.4
Calcium infusion	3	60 (47–75)	41 (24–56)	11 (7–15)	63.9 ± 1.9	64.9 ± 2.0	37.7 ± 0.4	38.1 ± 0.5
Atropine sulfate	3	41 (35–46)	42 (24–61)	15 (9–18)	69.1 ± 6.1	63.4 ± 5.2	37.9 ± 0.2	38.2 ± 0.4
Morphine	5	74 (59–87)	26 (21–38)	16 (7–29)	77.4 ± 5.9	55.0 ± 3.7‡	38.2 ± 0.1	37.3 ± 0.1‡

*BSA = body surface area.
†After 48 hours of salicylate administration.
‡$p < 0.05$.

Nitrogen loss, like energy expenditure, is related to the size of the injury or extent of infection, decreases with time, and usually becomes positive with resolution of the stress. The alteration in protein metabolism thus correlates closely with changes in oxygen consumption and energy utilization, and nitrogen contributes a constant 15 to 20 per cent of the metabolic fuel oxidized under a variety of metabolic conditions.[10] Increased excretion of urinary nitrogen is accentuated by bedrest, poor nutritional intake, lack of muscle exercise, an ambient temperature below 25°C, and anesthesia, but these factors are only additive to the basic reset in the protein metabolism which occurs following injury.

When Cuthbertson concluded his earlier studies on protein catabolism following injury, he commented that the nitrogen subsequently lost from the body came from systemic stores, rather than arising from damaged tissue at the injury site. Others have confirmed this concept, and most evidence suggests that the main source of catabolized protein is from skeletal muscle: this conclusion is based on the magnitude of nitrogen lost, the clinical evidence of muscle wasting and decreased strength, serial body compositional measurements, and muscle biopsies in humans and carcass analysis in small animals.

The mechanism and mediators of the increased nitrogen loss following injury have only recently been clarified. Cahill and associates studied proteolysis and gluconeogenesis in starvation and found that amino acids (primarily alanine) are released from the muscle bed, transported to the liver, and converted to new glucose. This provides a constant flow of a readily available fuel to maintain function of essential glucose-dependent tissue.[5] Because glycogen stores are limited and fatty acids cannot be converted to new glucose, this alanine cycle provides an ongoing supply of glucose at the expense of body protein. Increased gluconeogenesis and ureagenesis thus reflect the body's protein catabolic response to injury, and this same sequence of metabolic events occurs with infection, prolonged exercise, and cold exposure.

What are the signals which regulate muscle proteolysis? Skeletal muscle breakdown is influenced by hormonal environment, passive and active contractions, and availability of nutrients. Insulin appears central to the regulation of protein metabolism and relative changes of plasma insulin levels are associated with muscle amino acid uptake or release.[4] Glucagon does not appear to have a peripheral effect on amino acid release but acts centrally on the liver.[12] Catecholamines stimulate an outpouring of lactic acid from muscle, and this is followed by an efflux of three-carbon amino acid fragments which shuttle carbon intermediates to the liver for conversion to new glucose. Glucose then moves back to the muscle and is converted to pyruvate in the skeletal muscle cell. This three-carbon intermediate may receive an amino group from the branched chain amino acids which are oxidized in muscle (Fig. 7). The new three-carbon nitrogen containing compound, alanine, moves back to the liver with other three-carbon intermediates and is reconverted to new glucose; the nitrogen residue is simultaneously processed to urea. Thus, the rate of ureagenesis (reflected by urinary excretion of the urea) generally correlates with the rate of gluconeogenesis.

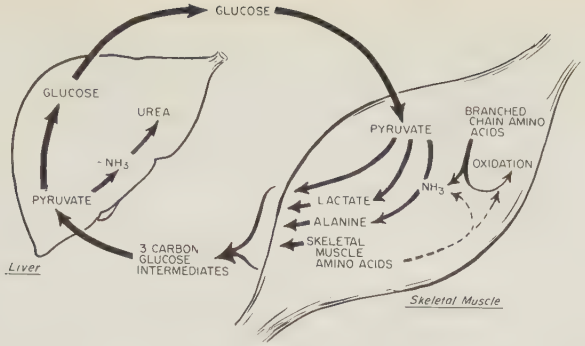

Figure 7. Six carbon-three carbon cycling mediated in the post-traumatic state provides a shuttle system from the periphery to the liver for synthesis of new glucose and proteins. The energy costs of this cycle system are reflected in post-traumatic metabolism.

As previously noted, hepatic gluconeogenesis is directed by an interaction of hormones; insulin favors hepatic glucose storage, and catecholamines, augmented by glucagon and glucocorticoids, signal for hepatic glucose production. The increased sympathetic activity directs the response of the endocrine pancreas hormone which in turn regulate the disposition of key substrates under their control. Mobilization of substrate from the periphery is stimulated by catecholamines and this "signal for mobilization" is increased with insulin deficiency. Thus, increased adrenergic activity again appears as the major mediator of the metabolic response following injury or infection, stimulating not only calorigenesis but regulating substrate mobilization (through the Cori and alanine cycles) and controlling hepatic gluconeogenesis.

Altered Glucose Kinetics

Hyperglycemia commonly occurs in critically ill patients, and the elevation of fasting blood sugar above normal is generally related to the severity of injury or infection. Oral or intravenous glucose tolerance tests in patients following hemorrhage, burn shock, or systemic infection demonstrate prolonged elevations in blood glucose concentrations, characteristic of the "diabetes of injury." Long and associates demonstrated increased flow of glucose through the extracellular fluid compartment in critically ill patients,[23] and hepatic catheterization studies suggest that insulin inhibition of hepatic gluconeogenesis is dampened following injury.[15]

In burn patients, the volume of the glucose space, the instantaneous proportionality constant for glucose disappearance (k), and the mass flow of glucose through the glucose space ($\dot{Q}$) were determined, using the model of Hlad and Elrick.[16] Insulinogenic index, described by Seltzer and associates[32] was also determined following the injection of a 25 gm glucose load.

During the initial period of burn shock, body glucose was elevated, but mass flow of glucose through the expanded glucose space (extracellular fluid compartment) was only slightly greater than normal (Table 3). As

Table 3. *Glucose Kinetics in Burn Patients*

	N	$\dot{Q}$ (MG PER KG PER MIN)	K ($100\ MIN^{-1}$)	BODY GLUCOSE (MG PER KG)	SERUM GLUCOSE (MG PER 100 ML)
Normals	12	3.92 ± 0.32	4.01 ± 0.58	106 ± 5	70 ± 2
Resuscitation	4	5.81 ± 0.44	1.21 ± 0.12	483 ± 22	140 ± 11
Burns (6–16 days)	17	10.12 ± 0.95	5.27 ± 0.51	200 ± 11	113 ± 5

the integrity of the extracellular fluid compartment was re-established and normal circulation was achieved following resuscitation, the patient moved from the ebb phase of injury to the flow phase. At this point in time (6 to 16 days postinjury), the rate of glucose disappearance was enhanced, the proportionality constant for glucose disappearance was similar to that obtained in normal individuals, in spite of persistent hyperglycemia which was observed in the burn patients. Glucose flow was significantly elevated in the burn patients compared to the normal individuals, suggesting that the increase in blood glucose observed in these individuals is a consequence of increased hepatic production of glucose, not altered peripheral disappearance, as determined by the proportionality constant for glucose disappearance.[42] Glucose flow was related to the extent of injury and fell with time postinjury to return to normal levels with closure of the burn wound.

The insulin response to glucose was dampened during burn shock resuscitation, but was comparable to the response seen in normal individuals when evaluated during the height of the hypermetabolic response.[45] Unger and Orci, in proposing the bihormonal control of glucose, suggested that the major role of insulin was in controlling the entry of glucose into peripheral tissues.[36] Although insulin decreases hepatic glucose output in normal man, this insulin effect on the liver is greatly dampened during states of high glucose production. In this group of critically ill injured patients, the instantaneous proportionality constant for glucose disappearance was related to the insulin response as previously described in normal and diabetic patients (Fig. 8). Glucose entry into the periphery was not related to fasting insulin level, but correlated with the early or total insulin response.[45]

These findings demonstrate that increased sympathetic activity does not always cause significant inhibition of insulin release to a glucose load in stressed man. These data are compatible with our knowledge of sympathetic control of the endocrine pancreas. During burn shock resuscitation, alpha receptor inhibitory effects appear dominant, insulin and diabetic-like glucose tolerance curves are observed. As the injured patients become hypermetabolic, profound beta adrenergic receptor effects are observed, characterized by increased basal heat production. At this time, normal concentrations of fasting insulin and appropriate insulin response to glucose are observed.[45] Subtle adjustments in the sympathetic and parasympathetic nervous system reflect these alterations in metabolic control, with both alpha and beta adrenergic receptor effects observed in the ebb phase (shock phase) of injury while beta receptor effects dominate during the hypermetabolic or flow phase of injury. A

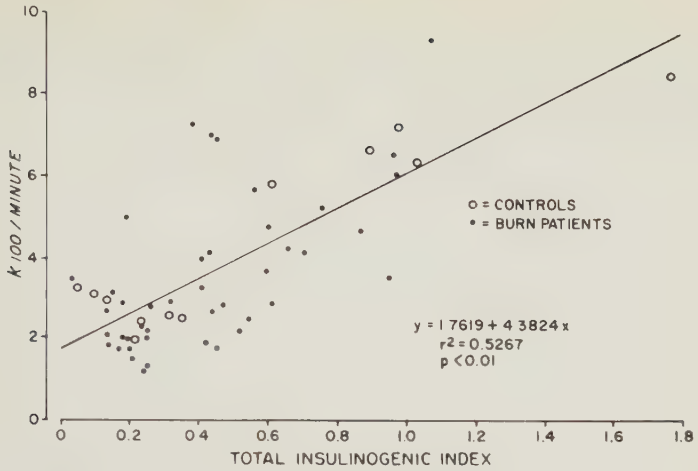

Figure 8. The insulin response is related to glucose disappearance in normals and thermally injured man.

characteristic effect of the flow phase of metabolism is the increased movement of a large mass of glucose from the liver to the peripheral tissues.

INTERACTIONS BETWEEN HEAT PRODUCTION, NITROGEN LOSS, AND GLUCOSE FLOW: AN INTEGRATION OF THE BODY'S HOMEOSTATIC RESPONSE TO INJURY

Both heat production and glucose flow increase with the extent of injury, and these two factors also appear to change together with time following injury. Simultaneous measurements of glucose flow and oxygen consumption performed in 10 normals and 17 burned patients demonstrate a close relationship between the mass flow of glucose through the extracellular compartment and heat production (Fig. 9). However,

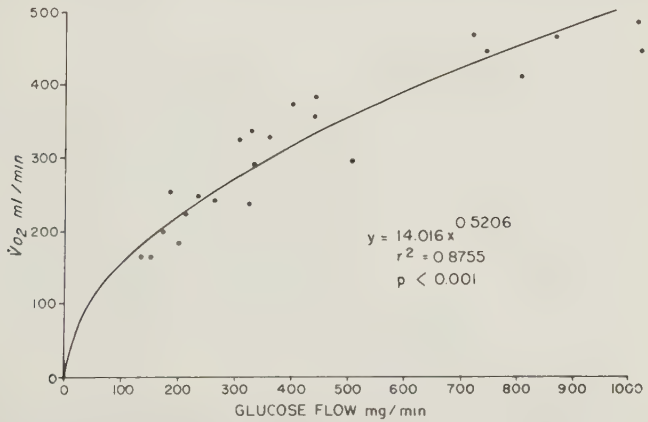

Figure 9. Oxygen consumption is closely related to mass flow of glucose through the intracellular space.

this relationship did not occur because glucose was oxidized as a primary fuel source; in contrast, all the respiratory quotients of these patients studied were low (0.70–0.78), reflecting the oxidation of fat as the primary fuel substrate.

Increased flow of glucose from the liver to the periphery occurs during the hypermetabolic, reparative, or flow phase of injury. The glucose appears to be converted to three-carbon intermediates which return back to the liver for resynthesis to new glucose, utilizing metabolic pathways described by the Cori cycle and alanine shuttle system. Entry of glucose into the tricarboxylic acid cycle is limited, a finding consistent with earlier studies which suggest a partial block in metabolic pathways leading from three-carbon to two-carbon fragments following operative injury.[9] Enzymes which favor conversion of three-carbon intermediates to glucose are pyruvate carboxylase and phospholenopyruvate carboxylase: increased synthesis of these enzymes occurs in the presence of high levels of glucocorticoids, glucagon, and catecholamines, and low levels of insulin, precisely the hormone environment present during the catabolic phase of injury.

Heat production at the cellular level appears to be regulated by ATP hydrolysis and ADP stimulated substrate oxidation. In heat generating biologic systems, ADP is the most critical substance for determining the respiratory rate of mitochondria, a regulatory process known as acceptor control.[17] The cycle of glucose metabolism is an energy requiring process utilizing ATP and generating ADP. Oxygen consumption is closely related to the rate of glucose flow through the extracellular space, but this occurs at a time when glucose is not the major fuel source being oxidized. The following hypothesis provides one explanation for this relationship. ADP generated by the cycling of glucose closely controls the rate of fuel oxidation; hence heat production and oxygen consumption can be related to glucose cycling through the ATP-ADP shuttle system (Fig. 10). The glu-

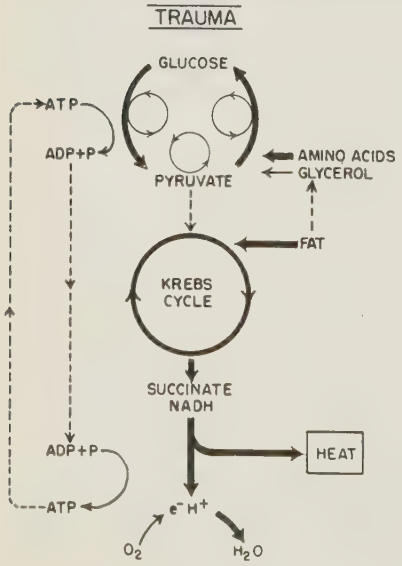

Figure 10. The entry of three-carbon fragments in the Krebs cycle is related by key enzymes under hormonal control which favor formation of new glucose. Thus, the six carbon-three carbon cycle "spins" while the Krebs cycle oxidizes two-carbon fragments from fat. The two cycles are interrelated by the ADP control mechanism: the amount of ADP generated by glucose cycling is related to oxygen consumption through receptor control mechanisms.

cose utilized during the mass flow of six-carbon substrate through the body is replaced by skeletal muscle amino acids that replenish the amount of glucose utilized. Critical to the understanding of body homeostasis to injury and still unanswered is why the peripheral tissue of the critically ill surgical patient requires this large mass flow of glucose.

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Fluid, Electrolyte, and Acid-Base Balance

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Volume and distribution of body water, and concentration of electrolytes in the plasma and interstitial fluid and within cells are controlled by a precise system of regulatory mechanisms that maintain both intra- and extracellular volumes and concentrations of ions within narrow limits. Regulation of water intake by thirst, and of electrolytes by the variety of foods ingested, and to some degree taste and habit, are coordinated with renal regulation of volume, tonicity, and electrolyte concentration to achieve normal fluid and electrolyte balance.

Control of the concentration of hydrogen ion, the pH of body fluids and cells, depends on regulatory mechanisms that normally maintain plasma pH within very narrow limits. Respiratory regulation of partial pressure of carbon dioxide, and renal regulation of fixed acid anions and plasma bicarbonate concentration, together with a complex of buffer systems both extra- and intracellular, maintain acid-base balance precisely despite a wide variation of both ingested and metabolic acid loads.

This discussion considers body composition including body cell mass and supporting and protecting tissues; fluid compartments and their size, composition, and function; metabolism of water and electrolytes, and the regulatory mechanisms that defend the volume, content, and acid-base balance of the body. With these as background, alterations in water balance, in electrolyte composition and distribution, and acidosis and alkalosis are analyzed. Parenteral fluid and electrolyte therapy are discussed as an alternative and often necessary means of maintaining or correcting abnormalities in fluid, electrolyte, and acid-base balances.

A thorough understanding of the physiologic principles underlying fluid, electrolyte, and acid-base balance and of the compensatory mechanisms that come into play when disease, trauma, sepsis, or surgery distort normal patterns is essential, if the surgeon is to recognize malfunction where he sees it, and take appropriate steps to correct it. Failure to do so substantially increases both morbidity and mortality in seriously ill patients.

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NORMAL BODY COMPOSITION

Essential to an understanding of the requirements of the surgical patient for parenteral therapy is knowledge of what constitutes normal body composition.

Although chemical analysis of the elements which make up the human body has been reported by a number of different investigators over the past 75 years, surgery is particularly indebted to Moore and his associates who, using isotope dilution techniques as well as chemical analyses, have determined not only the chemical composition of the body, but, more importantly, its functional compartments. The range of normal body composition in both males and females over a wide span of age has been established, and abnormal changes in body composition resulting from disease or injury have been evaluated.

Total Body Water

The largest single component of the body is water. Body water is distributed throughout the cells, the extracellular fluids, and the solid supporting structures. The highest concentration of water is present in metabolically active cells of muscle and viscera, the lowest in relatively inert and inactive supporting structures such as the skeleton. Isotope dilution studies using either heavy water (^2H_2O or D_2O) or tritiated water (^3H_2O) have shown that in the normal adult male, under the age of 40, approximately 60 per cent of body weight is water. In young women the exchangeable body water averages about 50 per cent of body weight, chiefly because the percentage of fat is higher than in men and the percentage of skeletal muscle is lower. In both sexes there is considerable normal variation of total body water content which makes accurate prediction of total body water difficult in a given individual. In the studies of Moore and his associates,[19] total body water is expressed as regression equations based on total body weight. Table 1 presents data from studies

Table 1. *Total Body Water (TBW) by Sex and Age**

SEX	AGE GROUP (YEARS)	SUBJECTS	MEAN BODY WT (KG)	MEAN TBW (LITERS)	95 PER CENT CONFIDENCE LIMITS OF MEAN AS PER CENT OF MEAN	RATIO (PER CENT) TBW(L) TO WEIGHT (KG)
Male	16–30	63	71.75	42.26	±16	58.9
Male	31–60	56	73.57	40.24	±17	54.7
Male	61–90	13	69.42	35.82	±16	51.6
Female	16–30	54	60.89	30.99	±13	50.9
Female	31–90	34	62.62	28.36	±21	45.2

Predicted normal:

$$\text{Males: } \frac{\text{TBW in L}}{\text{body wt in kg}} \times 100 = 79.45 - 0.24\,(\text{Wt}) - 0.15\,(\text{age})$$

$$\text{Females: } \frac{\text{TBW in L}}{\text{body wt in kg}} \times 100 = 69.81 - 0.2\,(\text{Wt}) - 0.12\,(\text{age})$$

*Data in Tables 1–5 from Moore, F. D., et al.: Body Cell Mass and Its Supporting Environment. Philadelphia, W. B. Saunders Co., 1963.

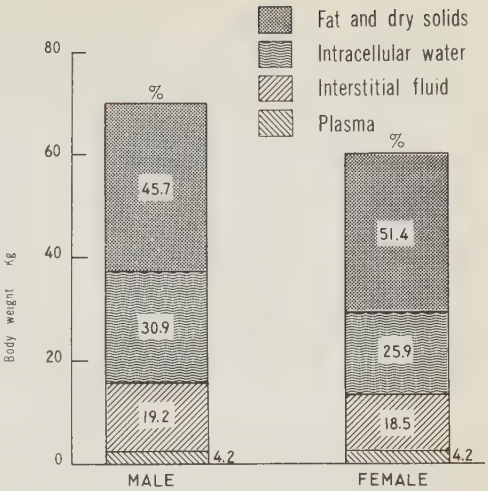

Figure 1. Body composition as percentage of body weight in adult males and females. Body water is shown as intracellular water, interstitial fluid, and plasma water. Total body water is the sum of the three divisions of water distribution. Because the fat-free body is 73.2 per cent water, body fat may be calculated as per cent body fat + $\frac{\text{per cent body water}}{0.732}$ = 100 per cent. Data from Moore.[19]

of 132 normal males and 88 normal females. Each series is divided to show differences due to age. Significant differences in regression equations exist for each group. There is a gradual and significant decline with age in total body water as a percentage of body weight.

Figure 1 illustrates the proportions of body weight as total body water in average size normal adult men and women, and its distribution as ICW, interstitial fluid, and plasma. Comparison of this figure with Figure 2 indicates the major differences in water content and distribution that exist between adults and infants and emphasizes a reason for the special problem of water and electrolyte balance in infants.[19, 34]

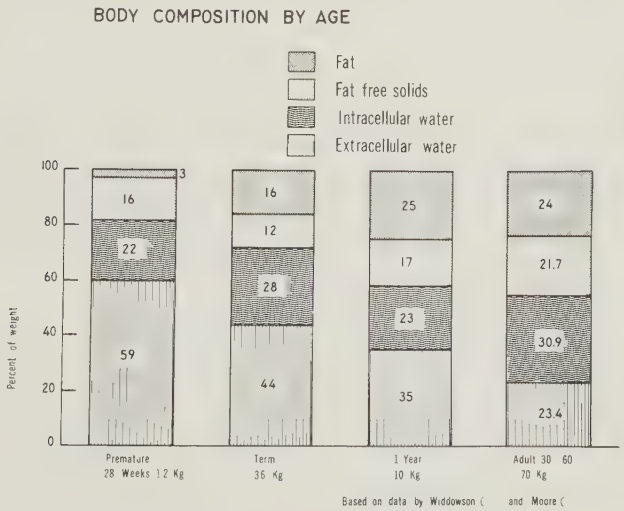

Figure 2. Body composition by age, showing progressive decrease in body water from very high percentage of weight in premature and term infants, to adult levels of approximately 55 per cent of body weight. Fat and fat-free solids increase proportionately. Intracellular water increases as body cell mass becomes larger, while extracellular water decreases. All are shown as per cent of body weight. Data from Widdowson[34] and Moore.[19]

Total body water may be considered as being distributed in two major compartments or spaces, based on differential concentration of the two major cations, sodium and potassium, and by the volume represented by dilution of radioactive isotopes, or other substances which appear to reach equilibrium in a portion of the total water pool.[19] The two major compartments are intracellular water (ICW) and extracellular water (ECW). Intracellular water is that portion of TBW within cells. Body composition studies indicate that from 50 to 58 per cent (average 55 per cent) of TBW is intracellular in normal healthy adults. Lean individuals with a relatively large skeletal muscle mass, such as trained young male athletes, have a higher percentage of TBW within cells, while females tend to have a more nearly equal distribution of TBW between ICW and ECW.[20]

Extracellular water consists of the water component of the extracellular fluids, plasma, interstitial fluid, and the water component of extracellular solids including tendon, fascia, dermis, collagen, elastin, and skeleton. Since there is no way of distinguishing in vivo among the various areas of distribution of ECW, except for measurement of plasma volume and total ECW, ECW is usually considered as a two subcompartmental distribution of interstitial fluid and plasma.

The size of the ECW compartment as a volume or space depends upon methods used for measurements, and varies from 15 to 16 per cent of body weight when inulin, sucrose, or mannitol is the indicator; it is as high as 27 per cent of body weight if ^{24}Na is assumed to be distributed entirely extracellularly, which it is not. Measurement of other small ions, such as $^{35}SO_4^{=}$ and $^{82}Br^{-}$, gives equilibration values of distribution of from 21 to 26 per cent of body weight for ECW; these data suffer from the fact that these ions enter into cells to some degree with time. As a practical matter, ECW can be considered as 23 *per cent of body weight* in normal adults, or even as 20 per cent of body weight as is commonly used clinically for extracellular fluid estimation in water and electrolyte balance problems.

The Major Electrolytes: Sodium, Chloride, and Potassium

TOTAL BODY SODIUM. The sodium ion content of the normal human body is stated to be from 52 to 60 mEq per kg in the adult male, and 48 to 55 mEq per kg in the female. A 70 kg man would therefore have from 3600 to 4200 mEq (83 to 97 gm) of sodium. From 35 to 40 per cent of the total body sodium is in the skeleton, and 65 to 75 per cent of skeletal sodium is unexchangeable or very slowly exchanged with that in body fluids and isotope tracers.[31]

TOTAL EXCHANGEABLE SODIUM (Na_e). Na_e is the pool of sodium within the body with which $^{24}Na^{+}$ or $^{22}Na^{+}$ comes into equilibrium, as usually measured at 24 hours after administration of the isotope. It is about 65 per cent of total body sodium and does not change significantly with age or sex in normal adults. Na_e per kg is lower in females than in males since the former have a higher percentage of body fat. Individual variation in Na_e is considerable and is a function of body composition. Average Na_e in normal adult males and females is given by Moore et al.[19] (Table 2).

Table 2. *Average Exchangeable Sodium (Na_2) in Normal Adult Males and Females*

	AGE GROUP (YRS)	NUMBER	NA_e (mEq PER KG)	95 PER CENT C.L.* (PER CENT OF MEAN)
Males	16–84	149	40.5	±21
Females	16–90	78	37.1	±17

*Confidence Limits

RESIDUAL SODIUM. The portion of exchangeable sodium not accounted for by the product of extracellular water volume (ECW) and extracellular water sodium concentration in mEq per L is residual sodium. This averages 10 to 15 per cent of Na_e.

TOTAL BODY CHLORIDE. This averages about 33 mEq per kg in a normal adult male[5] so that a 70 kg man contains about 2300 mEq or 81.7 gm. Predominantly an extracellular ion, chloride is found in low concentration in bone and is probably loosely bound, but exchangeable, in connective tissue. Chloride is in part intracellular; the erythrocytes have the highest cellular concentration with gastric mucosa, gonads, and skin containing lesser amounts.

EXCHANGEABLE CHLORIDE (Cl_e). This is usually determined by equilibration with $^{82}Br^-$, although $^{36}Cl^-$ has been reported as a useful tracer.[32] Data for exchangeable chloride are given in Table 3.[19]

TOTAL BODY POTASSIUM. In the healthy young adult male this is stated to be from 42 to 48 mEq per kg body weight.[19] A 70 kg man would contain from 2940 to 3360 mEq (115 to 131 gm) of potassium. In trained athletes with larger than normal muscle mass, total body counting of ^{40}K gives values of 60 and 65 mEq per kg body weight.[20] Virtually all of body potassium appears to be exchangeable with ^{42}K in the normal adult in 24 hours. The only exceptions are erythrocyte potassium which is slowly exchanging, and the skeleton where the small amount present may not exchange fully. For practical use total body potassium and exchangeable potassium (K_e) are the same.

TOTAL EXCHANGEABLE POTASSIUM (K_e). This is the pool of potassium within the body which comes into equilibrium with ^{42}K in 24 hours.

Table 3. *Average Exchangeable Chloride (Cl_e) in Normal Adult Males and Females*

	AGE GROUP (YRS)	NUMBER	CL_e mEq PER KG	95 PER CENT C.L.* (PER CENT OF MEAN)
Males	16–90	67	29.4	±23
Females	16–90	60	26.4	±21

*Confidence Limits
Cl_e bears a specific relationship to Na_e such that $Cl_e = 0.7315\ (Na_e) - 16$.

Table 4. *Age- and Sex-Related Average Exchangeable Potassium (K_e) in Normal Adult Males and Females*

	AGE GROUP (YRS)	NUMBER	K_e (mEq PER KG)	95 PER CENT C.L.* (PER CENT OF MEAN)
Males	16–30	97	48.1	±23
	31–60	34	45.1	±20
	61–90	20	37.3	±16
Females	16–30	59	38.3	±20
	31–60	28	34.2	±23
	61–90	21	29.7	±29

*Confidence Limits

Approximately 98 per cent of K_e is considered to be intracellular. Since the potassium concentration of extracellular fluids averages 3.5 to 5.0 mEq per L, the total extracellular potassium in a 70 kg adult male is about 60 mEq.

Exchangeable potassium is higher in males in proportion to body weight, because of a larger muscle mass in males. It declines in both sexes as a function of age (Table 4).[19]

Na_e, K_e, AND TBW. The sum of K_e and Na_e, called "total base" by Moore et al.,[19] has a very high correlation with TBW when each of the three variables are measured independently by isotope dilution techniques. The regression equation for this relationship is:

$$Na_e(mEq) + K_e(mEq) = 163.19 \text{ TBW (L)} - 69$$
$$r = 0.99 \ (P < 0.001)$$

Unaffected by age groups or sex, this relationship permits close estimation of the third factor, when any two are known.* Na_e bears a close relationship to extracellular water in both males and females, as does Cl_e. K_e bears an even closer relationship to intracellular water, since the concentrations of K are very low in all extracellular fluids (4 mEq per L) as compared to the intracellular value which averages 150 mEq per L.

In healthy individuals, Na_e/K_e ratios approximate 0.85 in males and 1.0 in females. In a wide variety of illness, such as trauma, sepsis, cardiac or renal insufficiency, and prolonged inadequate nutrition whether due to failure of intake or to malabsorption, the Na_e/K_e ratio rises; values of 1.5/1 or higher are not unusual in debilitated or edematous individuals (Table 5).

Body Cell Mass and Extracellular Tissues

A functional consideration of normal body composition involves division of the body into its living cells, and their fluid and solid extracellular supporting structures (Fig. 3).

*See article by Shizgal in this symposium (Part II).

Table 5. *Formulas for Predicting Normal Values in Body Composition for the Adult*

1. *Total Body Water (TBW)*

   Males $$\frac{TBW_{(L)}}{\text{Body Wt. (kg)}} \times 100 = 79.45 - 0.24\ (\text{Body Wt.}) - 0.15\ \text{age}$$

   Females $$\frac{TBW_{(L)}}{\text{Body Wt. (kg)}} \times 100 = 69.81 - 0.26\ (\text{Body Wt.}) - 0.12\ \text{age}$$

2. *Intracellular Water (ICW)*

   Males $$\frac{ICW}{TBW} \times 100 = 62.3 - 0.16\ \text{age}$$

   Females $$\frac{ICW}{TBW} \times 100 = 52.3 - 0.07\ \text{age}$$

3. *Exchangeable Potassium (K_e)*

   Using ICW for males or females as appropriate

   $K_e(mEq) = 150\ (ICW_L) + 4(TBW - ICW)$

4. *Exchangeable Sodium (Na_e)*

   $Na_e(mEq) = 163.2(TBW_{(L)}) - 69 - K_e(mEq)$

5. *Exchangeable Chloride (Cl_e)*

   $Cl_e(mEq) = 0.7315(Na_e) - 16$

6. *Regression Equation for $Na_e + K_e$ on TBW*

   $Na_e(mEq) + K_e(mEq) = 163.19(TBW_{(L)}) - 69$

7. *Extracellular Water (ECW)*

   ECW = TBW − ICW

   ECW = Plasma Volume × 0.93 + Interstitial Fluid Vol. × 0.98

8. *Extracellular Fluid (ECF)*

   ECF = Plasma Volume + Interstitial Fluid

   ECF = ECW × 1.03

9. *Osmolar Balance*

   $$\frac{Na_e(mEq) + K_e(mEq)}{TBW_{(L)}} = 150$$

Body cell mass (BCM), a concept defined and developed by Moore et al.,[19] consists of all of the cells of the body, regardless of their location. All have a high intracellular potassium concentration, and all utilize chemical energy from food, or tissue catabolism, to perform thermal, chemical, and sometimes mechanical work. The body cell mass is not uniform in metabolic rate, in chemical, mechanical, or thermal work done, or in fuel requirements, since these vary from one cell type and location to another, and with the activity of the body.

Chemical analysis of representative samples of cellular tissues from man indicate a K/N ratio of very close to 3 mEq of potassium for each gm of nitrogen. Virtually all the potassium and a very high percentage of protein are intracellular. Assuming an average K/N ratio of 3 mEq per gm N, and a total net weight of average cells (excluding extracellular fluid) of grams N × 25,[19] body cell mass can then be calculated:

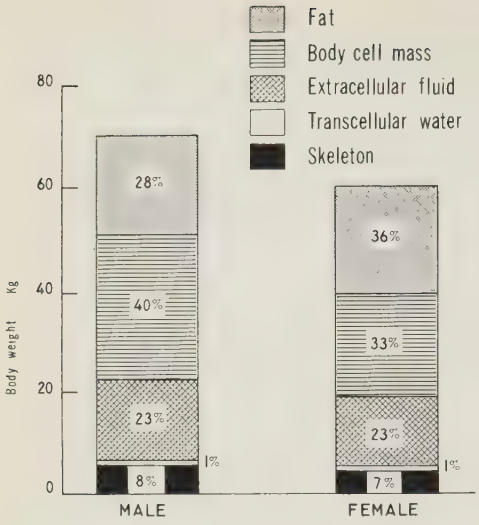

Figure 3. Body cell mass and its proportional relationship to supporting structures. Extracellular fluid includes the aqueous phase of noncellular elements of fascia and tendons as well as interstitial fluid and plasma. Transcellular fluid is fluid of joints, cerebrospinal fluid, and the content of the fasting gastrointestinal tract. Based on data from Moore.[19]

$$BCM = \frac{(K_e - ECK) \times 25}{3}$$

Since extracellular potassium (ECK) is relatively very small it can be ignored and therefore:

$$BCM_{gm} = K_e\,(mEq) \times 8.33$$

Intracellular water (ICW) can be calculated from K_e on the basis of $\frac{K_e(mEq)}{150} = ICW(L)$ in normals, since potassium concentration in intracellular water is approximately 150 mEq per L (149.7 ± 7.2). Intracellular K concentration can be adjusted for changes in extracellular fluid tonicity by adjustment of the equation $\frac{Na_e + K_e}{TBW} = 150$, a ratio which is an expression of the osmolar equilibrium between cells and extracellular fluids. As noted previously, ICW is normally 50 to 58 per cent of TBW, with males tending to have a higher percentage of TBW as ICW. The ratio $\frac{ICW}{TBW}$ is altered in a variety of diseases, almost all of which result in a decreased ratio by expansion of both TBW and ECW as a percentage of body weight, with or without loss of BCM as well.

Oxygen consumption and caloric expenditure are closely correlated with BCM. Kinney et al.[15] have measured oxygen consumption as 8 to 10 ml per min per kg BCM, and caloric expenditure as 2.7 to 3.6 Kcal per hr per kg BCM. Novak et al.[20] measured basal oxygen consumption of young athletes as 6.6 to 7.58 ml O_2 per min per kg BCM.

Creatinine excretions have been reported of 60 to 80 mg per kg BCM per day[15] and of 47 to 51 mg per kg BCM per day.[20] This author has become

doubtful of the value of daily creatinine excretion as a measure of skeletal muscle mass in seriously ill patients, having observed in many patients a striking fall in total creatinine excretion and in plasma creatinine levels following introduction of a high caloric-amino acid nutritional regimen.

This occurred whether the high caloric material was given intravenously or as chemically defined diets. Plasma creatinine levels of 0.4 mg per cent and total creatinine excretion in the urine of less than 0.5 gm a day in adults accompanied a positive nitrogen balance. These data suggest that some part of creatinine production is related to muscle catabolism.

Extracellular tissues (ECT) are those fluids and solids of the body that are wholly outside of cells. Even though some of these have extremely small cell components, only the extracellular part of such tissues is considered as ECT. Extracellular fluid (ECF) has been discussed. The extracellular solids include the skeleton, tendons, fascia, dermis, collagen, and elastin. Interstitial fluid comprises about three-fourths of total extracellular fluid and 15 to 18 per cent of body weight. Interstitial fluid is in intimate communication with plasma, being separated only by capillary walls which permit easy diffusion of all but large protein molecules. Its protein content is much lower and its water content is therefore higher than that of plasma, as are concentrations of chloride and bicarbonate as required by the Gibbs-Donnan distribution equilibrium. The plasma component of extracellular fluid varies between 3.5 and 5 per cent of body weight and averages 4.2 per cent. Normal protein concentration is approximately 7 gm per 100 ml, and therefore plasma is about 93 per cent water. Because of the lower water content of plasma and the presence of protein molecules which behave as nondiffusible anions, the concentration of cations in plasma water is higher than that in interstitial fluid, and the concentration of inorganic anions is somewhat lower.

Extracellular Solids. No measurement of extracellular water takes accurately into account the extracellular solids, of which the skeleton is the largest component. The skeleton is estimated to be 10.5 per cent of the normally hydrated fat-free body weight in health, which makes it of the order of 8 per cent of total body weight in males and 7 per cent total body weight in females of normal body composition (see Fig. 3). Skeletal bone contains about 30 per cent water. It also contains a substantial amount of sodium, 230 to 288 mEq per kg in fat-free dry cortical bone, of which 65 to 75 per cent is unexchangeable, and as much as 85 per cent not associated with chloride. Potassium content of bone is low.[19] A nomogram of skeletal weight based on K_e and K_e/FFS has been prepared by Moore and associates which is useful for more precisely estimating skeletal weight.[19] In wasting diseases, in which there is substantial loss of both BCM and fat, the skeleton becomes a much larger percentage of body weight.

Dense connective tissue of fascial sheaths and tendons together with other collagen in the body has been estimated to comprise 6 per cent of body weight in dogs and 2 to 3 per cent in man. Subcutaneously equilibrated, fat-free collagen of fascia in the dog has been shown by Fulton[11] to contain 70 per cent water, and 57 mEq Na^+ per kg, suggesting that 45 per cent of the water content is bound in such a way as to exclude sodium.

Extracellular solids are, therefore, not chemically homogeneous with extracellular fluids. Equilibria for water, sodium, chloride, and probably hydrogen ion within extracellular solids appear to be rather specific for the solid tissue considered. These observations are of importance when considering the behavior of ECF, particularly interstitial fluid, in derangements of acid-base balance and, particularly, with hypoxic hypoperfusion.

Electrolyte Concentration of Body Fluids

Figure 4, modified from the famous diagrams of Gamble,[12] illustrates the approximate composition of interstitial fluid and intracellular water in comparison with that of plasma with its more precisely known values. Table 6 gives the range of normal and the analytic error of laboratory determinations for the major electrolytes of plasma as usually determined in serum. Values in this table are from the literature and from our laboratories.[25] It should be remembered that there is both a range of values present in normal individuals and an error present in any laboratory determination. The ranges shown take into consideration both the normal variation and the 95 per cent confidence limits of the laboratory procedure in a well-run clinical laboratory. Repeating any laboratory test will reduce the probability of error due to the test. When laboratory reports do not help to confirm the clinical diagnosis or course, it is wise both to repeat the test and to re-examine and re-evaluate the patient.

Table 6. *Normal Electrolyte Concentration of Serum**

ELECTROLYTES	RANGE OF NORMAL INCLUDING LABORATORY-METHOD VARIANCE	RELIABILITY OF LABORATORY TEST–95 PER CENT CONFIDENCE LIMITS
Cations		
Sodium	136–145 mEq/L	± 3 mEq
Potassium	3.5–5.0 mEq/L	± 0.2 mEq
Calcium	4.5–5.5 mEq/L (9.0–11.0 mg per cent)	± 0.1 mEq
Magnesium	1.5–2.5 mEq/L (1.8–3.0 mg per cent)	± 0.04 mEq
Anions		
Chloride	96–106 mEq/L	± 2.0 mEq
CO_2(content)TCO_2	24–28.8 mEq/L	± 0.2 mEq
Phosphorus (inorganic)	3.0–4.5 mg per cent (1.9 to 3.25 as $H PO_4^=$)	Considerable variance due to analytic problem
Sulfate (as S)	0.8–1.2 mg per cent (0.5–0.75 mEq/L as SO_4)	Method dependent
Lactate	0.7–1.8 mEq/L (6 to 16 mg per cent)	Method dependent
Protein	6.0–7.6 gm per cent (14–18 mEq/L) Depends on albumin	Method dependent

*Taken from Randall, H. T.: Water, electrolytes and acid-base balance. *In* Goodhart, R. S., and Shils, M. E. (eds.): Modern Nutrition in Health and Disease, 5th ed. Philadelphia, Lea and Febiger, 1973. Used with permission.

Anion Gap

An approximation of the accuracy of determination of the sodium, chloride, and bicarbonate concentrations of the plasma or serum or the determination of the existence of a major electrolyte abnormality in the patient can be made by equating the serum sodium concentration (in mEq) with the sum of the chloride and bicarbonate concentrations (in mEq) plus 10 mEq.

$$\text{mEq Na} = \text{mEq } HCO_3 + \text{mEq Cl} + 10$$

Since the sum of the cations and the anions in any biologic system must be equal and since sodium ion is the major cation of extracellular fluid and of serum or plasma, most of the anions balance sodium. The anionic structure of serum or plasma is somewhat more complex than that of the cations, because of the presence of substantial amount of plasma protein, the molecules of which behave primarily as anions at the pH of plasma. The sum of bicarbonate (27 mEq) and chloride (103 mEq) equals all but 10 mEq of the normal sodium concentration (Fig. 5). The relationship between the sum of the two anions and the serum sodium concentration normally remains constant.

If the sum of bicarbonate and chloride and 10 mEq is *less* than ± 4 mEq of the sodium concentration on repeated examinations, then there has been the addition of substantial amounts of another anion:

1. $HPO_4^=$ and $SO_4^=$, as in renal insufficiency.
2. Lactic acid, as in hypoxia, hypoperfusion, and salicylate intoxication.
3. Keto acids, as in diabetic ketoacidosis.
4. Bromide replacing chloride.

Conversely, if HCO_3 + Cl + 10 is *greater* than sodium by more than 3 to 5 mEq, hypoproteinemia is the likely cause if laboratory error is ruled out.

Much less is known about intracellular fluid (ICF) than about plasma and interstitial fluid. Muscle cells, liver cells, and erythrocytes obviously contain different functional proteins within them and their electrolyte content is different as well. However, the body cell mass has certain characteristics which all its cells share in common and many of these are different from extracellular fluid. The major intracellular cations are potassium and magnesium and there is relatively little sodium. Bicarbonate ion is present within cells in less than one half the concentration in ECF. The predominating intracellular anions are organic phosphates, and protein in substantial amounts (Fig. 4). Approximately 23 per cent of BCM is protein.

The osmolality of intracellular fluid is generally considered to be about the same as ECF, since water diffuses freely into and out of cells as shown by isotope dilution. The only exception in man would appear to be the medullary area of the kidney, where an osmotic gradient nearly four times that of ECF, and presumably of renal tubular cells, is maintained.

The apparent discrepancy between the ionic concentration of intracellular water and extracellular fluid may in part be explained on the

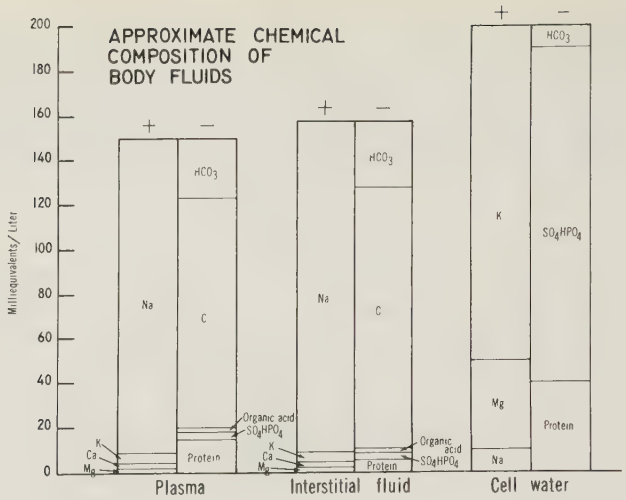

Figure 4. The electrolyte concentrations of plasma and interstitial fluid are compared with an approximation of the electrolyte content of cell water. Cell membranes maintain the striking concentration differences. Modified from Gamble.[12]

hypothesis that the bulk of intracellular water, and presumably electrolytes as well, is retained in the cell in a physical state different from that of a dilute aqueous solution (see Fig. 4). ATP is considered necessary to maintain layered binding of water to protein within the cell, a role that may be more important than providing energy for the sodium and potassium pumps.[17]

Forces Controlling the Water and Electrolyte Balance Between Cells and Extracellular Fluid

OSMOLALITY AND OSMOTIC PRESSURE. A substance in solution in water on one side of a semipermeable membrane which is freely permeable to water but through which the solute cannot pass exerts an effect such that water molecules tend to diffuse in larger numbers toward the solution side where the water molecule concentration (or activity) is less. Osmotic pressure is the physical force necessary on the solution side of the membrane to prevent the net movement of water across the membrane

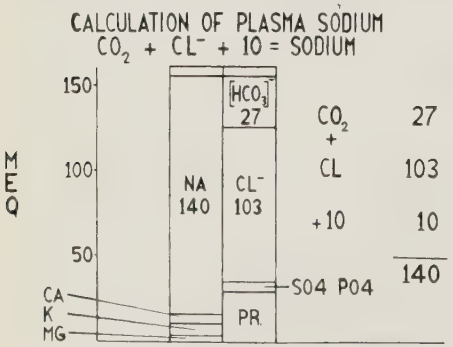

Figure 5. The anion and cation structure of normal plasma is such that the sodium concentration in milliequivalents is equal to the sum of $(HCO_3)^-$ + Cl^- + 10 mEq. The values should match within ± 4 mEq. Excluding laboratory error, if sodium is in excess of HCO_3 + Cl^- + 10, then an organic anion (lactate, ketoacids) or sulfate and phosphate are in excess. If sodium is lower, hypoproteinemia is the usual cause.

toward the solution and to maintain equilibrium. One gram molecular weight of a substance which does not dissociate into ions, such as glucose or urea, contains 6.06×10^{23} molecules and is termed 1 osmole; dissolved in 1 liter of water 1 osmole will require a pressure equal to 17004 mm Hg on the solution side to maintain equilibrium across a membrane permeable only to water. One milliosmole (mOsm or mO) is 1/1000th of an osmole and when dissolved in 1 liter of water has an osmotic pressure of 17 mm Hg.

Since the number of particles determines osmotic pressure, substances which ionize affect osmotic pressure according to the degree of dissociation. For example, sodium chloride dissociates into Na^+ and Cl^- in such fashion that at 0.154 molar concentration (that of body fluid), there are about 1.85 particles for each original molecule and these exert a pressure of 286 mOsm rather than 308 mOsm.[22]

Osmolality of a solution can be determined on the basis that 1 osmole dissolved in 1 liter of water will depress the freezing point of water by 1.86°C. Normal plasma or serum (fibrinogen molecules are very large so their absence makes virtually no difference) freezes at −0.533°C and osmolality is therefore $\frac{0.553}{186}$ or 297 mOsm. Freezing point depression osmometers are widely available in clinical laboratories today and are of great value in determining not only plasma osmolality but that of urine and other biologic fluids, thereby assisting the clinician in evaluation of fluid and electrolyte balance in his patients.

The permeability of cell membranes to various substances given parenterally, and the effect of commonly administered intravenous solutions on plasma osmolality and the balance between extracellular and intracellular water is of clinical importance in the management of fluid and electrolyte balance.

Urea, for example, is freely permeable through cell membranes and is normally evenly distributed in total body water. The normal BUN (blood urea nitrogen) of 20 mg per 100 ml (as 42.9 mg of urea per 100 ml) has an osmotic pressure of approximately 7 mOsm. A BUN of 100 mg per 100 ml means that there is 1 gm of urea nitrogen per liter or 2.14 gm urea with 35.7 mOsm osmotic pressure. The effect on cell hydration, however, is limited to the effect of urea as an osmotic diuretic and to changes in central nervous system hydration with sudden changes in concentration of urea in the extracellular fluid.

Glucose, on the other hand, is slowly permeable through cell membranes, and higher-molecular-weight sugars, such as sucrose and mannitol, remain almost entirely extracellular. A sudden increase in the concentration of any of these substances will increase the extracellular fluid osmolality, with a shift of water from cells to the extracellular fluid, and will also produce an osmotic diuresis when maximal renal tubular reabsorption is exceeded.

Hypertonic concentrations of either glucose or sodium salts, or a solution made hypertonic by the combined presence of sufficient glucose and sodium chloride, will result in a shift of water from cells to extracellular fluid. Excessive water administration usually as 5 per cent glucose

solution, in a patient with the reduced renal free water clearance commonly present following surgical treatment or other trauma, will reduce the extracellular osmolality as the glucose is metabolized and result in dilutional overhydration of cells and extracellular fluid.

The serum sodium under most circumstances is an accurate measure of plasma osmolality. Twice the serum sodium concentration in mEq plus 6 mOsm will closely approximate the plasma osmolality if excessive amounts of glucose or urea are not present.

The Metabolism of Water and Electrolytes—Water Balance

Man requires free water to maintain water balance. Even with maximum concentration of urine solutes, the water contained in the foods of a normal diet and the water produced by oxidation of food are inadequate to provide for urinary excretion of the end products of metabolism, and for losses of water from the bowel and vaporizing from the respiratory tract and skin. The amount of water and dilute liquids ingested daily varies widely with habit and climate, but in temperate climates averages 1000 to 2500 ml a day. Water in semisolid and solid foods averages 1000 to 1500 ml. Water of oxidation adds 200 to 400 ml a day. The average adult therefore adds a total of 2500 to 4500 ml of water daily to a body pool of 30 to 50 liters.

Loss takes place by four different routes: urinary output and the water content of stool, both of which are measurable, and by evaporation from the respiratory tract and from the skin; the latter two are measured only with great difficulty and are termed "insensible losses." In the normal individual water intake and loss balance very closely, and daily body weight fluctuates less than 2 per cent, and usually less than 1 per cent if determined at the same time of day. Insensible losses depend on body size, physical exertion, and on environmental temperature and humidity. In an environment of moderate temperature and humidity, losses are substantially less than in a warm humid environment where sweat loss becomes large. Respiratory insensible loss averages 300 to 500 ml per day in females and up to 750 ml per day in males. Surface evaporation and sweat together average 400 to 600 ml a day. Total insensible water loss is between 300 and 500 ml per meter^2 of body surface area per day, with minimal activity in a temperate environment.[4, 25, 27, 28] Sweat volume is small in a temperate climate except with vigorous activity, but may reach several liters a day, with serious losses of both water and sodium chloride, in warm humid environments with exposure to the sun.

Markedly obese patients have a much increased insensible water loss, largely as sweat. Brill[6] measured losses of 2.4 to 2.9 L a day in a group of markedly obese patients compared to an average loss of 0.9 L per day in normal individuals.

Daily or more frequent weighing of the individual is the only reliable method of keeping track of insensible losses. Combined with a record of measured intake and of urinary volume and bowel output, body weight permits reasonably accurate accounting of water balance on a day-to-day basis.

Urinary volume represents the difference between total water intake

plus water of oxidation and the sum of insensible losses plus the water in stool (normally 100 to 200 ml per day). Normal adults excrete from 1000 to 2500 ml of urine a day. Minimal urine volume with normal kidney function in a young adult is 400 to 600 ml per day. This requires the ability to concentrate the urine to a specific gravity of above 1.030 and with an osmolality of 1000 to 1400 mOsm. Urea represents more than one half of total solutes from a normal diet. Urea excretion is increased by high protein intake, and by trauma or sepsis which produces increased catabolism of body cell mass. A large protein intake or illness may substantially increase minimal urine volume. Renal disease increases the minimal volume required to clear a given solute load since the ability to concentrate the urine is diminished or lost.

Thirst is the mechanism for stimulating ingestion of water. A 1 to 2 per cent decrease in total body water is the usual stimulus, and represents a change of 350 to 700 ml in the normal adult. A decrease in intravascular volume as seen with acute hemorrhage, and the infusion or ingestion of hypertonic solutions are also effective stimuli to the sensation of thirst. The centers for control of thirst are located in the ventromedial and anterior hypothalamus, and are in close relationship to or overlap the centers of the neurohypophysis which regulate antidiuretic hormone (ADH).[16, 22]

ANTIDIURETIC HORMONE (ADH). As thirst is the regulator of input of water in man, so antidiuretic hormone has a fundamental role in the regulation of water balance and in control of water excretion. By altering the permeability to water of the cells of distal renal tubules and collecting ducts, ADH controls the amount of water reabsorbed and the volume of urine excreted. When ADH level is high in the plasma, the epithelium of the distal tubules and collecting ducts is more permeable to water, which diffuses from the tubules into the hypertonic medullary interstitium of the kidney and is thus returned to the circulation. When ADH levels are low, the distal nephron is relatively impermeable to water and a larger volume of urine of a lower osmolality is excreted. With severe reduction in plasma ADH, as occurs with injury to the neurohypophysis, very large volumes of very dilute urine are excreted necessitating ingestion of many liters of water a day to prevent dehydration from this state of diabetes insipidus.

Table 7 summarizes the factors which are known to stimulate or inhibit ADH secretion.

Inappropriate secretion of ADH results in major alteration of body fluid balance through water retention. The clinical findings, as discussed by Bartter and Schwartz[3] are: (1) hyponatremia with hypo-osmolality of the plasma; (2) continued renal excretion of Na^+ despite hyponatremia; (3) absence of clinical evidence of volume depletion; (4) urine less than maximally dilute; (5) normal renal function and adrenal function.

The primary causes of the syndrome of inappropriate secretion of ADH include tumors (particularly cancer of the lung or pancreas which synthesize ectopic ADH); injury, infection, trauma, or tumors of the brain or its meninges; pulmonary infection of severe degree, often with cavity formation; the postoperative state with anesthesia and sepsis; and, most commonly, injudicious overloading of patients with parenteral dextrose

Table 7. *Factors Which Stimulate or Inhibit Release of ADH**

	STIMULATE	INHIBIT
Osmotic	Hyperosmolar extracellular fluid	Hypo-osmolar extracellular fluid
Nonosmotic	Decreased carotid artery and aortic blood pressure via baroreceptors	Elevated blood pressure
	Decreased tension in left atrial wall and pulmonary veins	Increased left auricular pressure
	Emotional stress or pain	
	Quiet standing	Supine position
	Elevated temperature of blood	Cold, ↓ Blood temperature
	Drugs: Acetylcholine, morphine, meperidine, barbiturates, nicotine	Alcohol, diphenylhydantoin, epinephrine? atropine?
	? low oxygen saturation via carotid body	
	Low plasma volume or ECF	

*Taken from Kleeman, C. R., and Fichman, M. P.: The clinical physiology of water metabolism. N. Eng. J. Med., 277:1300, 1967. Used with permission.

and water. (See overhydration, hypotonicity, and water intoxication in the discussion which follows.)

An excellent review of regulation of body fluids by Shore and Claybaugh[28] is recommended as a resource for greater detail.

FLUID AND ELECTROLYTE REQUIREMENTS IN SURGICAL PATIENTS: CLINICAL APPLICATION

The purpose of administering parenteral fluids and electrolytes is to prevent deficiencies that otherwise result from inability of the patient's gastrointestinal tract to fulfill its normal functions. Also, in acute trauma and when there has been a substantial loss of water, electrolytes, or both from the body without adequate replacement, parenteral fluid therapy is required to restore a normal distribution of body fluids.

The requirements for parenteral therapy can conveniently be considered in three categories:

1. *Baseline requirements*: What does the patient require in water, electrolytes, basic calories, and micronutrients to minimize the effects of dehydration and of starvation due to cessation or reduction of oral intake? The calculation of baseline requirements disregards any preexisting dehydration or any abnormal losses, but baseline volumes may require modification in patients with extracellular fluid excess or dilutional hyponatremia.

2. *Abnormal losses*: What does the patient require in order to replace ongoing abnormal fluid and electrolyte losses resulting from the disease or its treatment, or both?

3. *Deficits or excesses*: What deficits (or excesses) does the patient have in water, electrolytes, blood volume, plasma proteins, and micronutrients? What should be done to correct these abnormalities, and at what rate should reconstitution be effected?

The daily or, in the case of the seriously ill patient, more frequent orders that are written for parenteral fluid and electrolyte therapy take into consideration all three of these major categories. The parenteral

fluids required are the sum of baseline requirements and abnormal losses plus (or excesses minus) a part of or all the deficits existing at the time treatment is begun.

A patient with a normal body temperature, living in a comfortable environment of both temperature and humidity, will lose between 800 and 1000 ml of water per day as insensible loss. The rate of loss is somewhat higher in men than in women and is proportionate to body surface area and to respiratory minute volume. Almost all of normal insensible loss is electrolyte-free. There is a small insensible loss of sodium, potassium, and chloride due to a combination of minimal sweating and to electrolyte lost in desquamation of the epidermis. Balance studies have suggested an insensible loss of approximately 20 mEq of sodium per day, an equal amount of chloride, and between 5 and 10 mEq of potassium.

Thus the normal average-sized adult, the idealized 70 kg young adult male, will require between 2000 and 2500 ml of water per day to provide for urinary output and insensible loss.

ENDOGENOUS WATER CONTRIBUTION. A part of this requirement will be obtained through metabolism of body tissues in a semistarving state. Endogenous water is derived from skeletal muscle mass which is 73 per cent water and contains protein which is oxidized for fuel, and from the oxidation of body fat stores. Endogenous water derived from muscle approximates 800 to 850 ml for each kilogram of body cell mass lost. This water is almost completely sodium-free and is rich in potassium, magnesium, phosphates, and sulfates.

Oxidation of fat provides slightly more than 1 ml of water per gm of fat oxidized. Moore estimates that about 10 ml of water is available for each 100 kcal which is derived from the burning of body tissues, part of which is fat and part body cells. The daily caloric requirement of the surgical patient depends in part upon sex and age but much more upon the extent and type of trauma, the presence of infection, the degree of immobilization, and the amount of energy required to maintain body temperature in the presence of abnormal evaporative water losses, either from hyperventilation or from exposed incompetent skin, as seen in the open treatment of burns.

The daily caloric requirement of the afebrile patient at bed rest will vary from 1500 to 2300 kcal, 400 or 500 of which is usually provided by the administration of glucose. The baseline production of endogenous water in this situation will be from 150 to 200 ml, or about 10 per cent of the total daily requirement. However, fever, trauma, infection, and immobilization greatly increase endogenous water production, and the seriously ill patient suffering from extensive trauma or massive infection may provide as much as 1000 ml of sodium-free, potassium-rich endogenous water a day. This must be taken into account in considering fluid balance.

ESTIMATION OF BASELINE REQUIREMENTS

Normal baseline parenteral water requirements vary from 1250 to 3000 ml per day depending on body cell mass size, age, and sex. Table 8 illustrates methods for estimating the baseline parenteral or combined parenteral and oral fluid requirements for surgical patients.

Table 8. *Baseline Fluid Requirements—Temperate Climate*

	AGE	AVERAGE WATER REQUIREMENTS
I. ADULTS—BASED ON "IDEAL" WEIGHT FOR HEIGHT AND AGE		
Average adults	25 to 55	35 ml per kg per day
Young active adults	16 to 30	40 ml per kg per day
Older patients	55 to 65 ±	30 ml per kg per day
Elderly	> 65 years	25 ml per kg per day
II. FOR CHILDREN OVER 5 KG BODY WEIGHT TO AGE 18*		
First 10 kg of body weight		100 ml per kg per day
Second 10 kg of body weight		50 ml per kg per day
Weight above 20 kg		25 ml per kg per day

*Infants and young children under 10 kg require special consideration. See Kiesewetter[14] for an example.

Body Weight

This is the most practical index of the state of hydration and of water balance. A number of different types of scales are available on which the patient may be weighed in the supine position, and one of these should be on every surgical floor in a modern hospital. Daily weights of patients on parenteral fluid therapy, with inevitable accompanying caloric insufficiency, should decrease with a weight loss of approximately from 0.3 to 0.5 per cent of body weight per day until adequate oral nutrition is instituted. Exceptions occur with blood transfusions, with deliberate changes in hydration, and during the first 24 to 48 hours following trauma or operation with local sequestration of fluid and increased parenteral therapy to compensate for it. The patient who gains weight in circumstances other than these while on routine parenteral therapy is almost certainly being overhydrated. The patient who rapidly loses weight, except during the normal post-traumatic diuresis, has usually had an abnormal loss which has been underreplaced.

Daily or more frequent body weight measurements are the single most important method of controlling water balance.

Factors Modifying Requirements

Factors which increase baseline requirements are essentially those which increase the insensible loss.

FEVER. Fever increases the baseline water requirements largely through hyperventilation with increased water evaporation. A patient with a fever of 103°F will require about 500 ml of additional baseline water per day. Endogenous water production is also increased.

EXCESSIVE SWEATING. A rule of thumb with respect to sweat loss is to increase the average adult baseline water requirements by 500 ml per day for each 5° above 85°F of ambient temperature. This is dependent on the humidity. Sweat is about one-third isotonic sodium chloride in the

summertime and nearly two-thirds isotonic in winter, so that additonal salt must be provided in baseline therapy to compensate. When the environmental temperature approaches body temperature, the seriously ill patient should be cooled, preferably by air conditioning, because insensible loss of water becomes very large when the ambient temperature exceeds body temperature. Grossly obese patients have substantially increased water loss through sweating—and will require additional free water.

Increased Metabolism. Hyperthyroidism increases the baseline water turnover substantially, as it does caloric requirements. Hyperthyroid patients in the semistarving state tend to consume massive amounts of lean body tissue and body fat, producing unusual amounts of endogenous water, and simultaneously to lose water both by respiratory evaporation and skin sublimation as well as by sweating.

Factors Which Reduce Baseline Water Requirements

These include reduced metabolic activity, as seen in hypothyroidism, in the elderly, and in situations in which there is an excessive amount of body water with overexpanded extracellular fluid space as in cardiac edema, in hypoproteinemia with starvation, in prolonged infection, in carcinoma of the gastrointestinal tract, and in the special circumstances of acute renal failure.

Baseline Electrolytes

The normal intake of sodium, potassium, magnesium, and chloride varies considerably with dietary habits. In metabolic balance studies done on patients prior to elective surgical therapy, the average daily sodium intake ranged from 75 to 120 mEq, potassium from 65 to 88 mEq, magnesium from 15 to 25 mEq, and chloride from 85 to 145 mEq.

In the absence of abnormal losses or of dehydration and salt deficits, the baseline sodium requirements of the average adult are easily met by a maximum of 500 ml of 0.9 per cent sodium chloride with 5 per cent dextrose. This provides 76 mEq each of sodium and chloride ion. In addition, 40 mEq of potassium chloride per day for all adults except those suffering from acute dehydration or renal insufficiency will provide sufficient baseline potassium to prevent many problems of potassium depletion. Potassium chloride should not be administered in concentrations in excess of 40 mEq per L of fluid, and therefore the baseline requirement should be dissolved in at least 1000 ml of otherwise isotonic infusion fluid.

In children, 3 mEq of sodium and 2 mEq of potassium per kg per day, up to 20 kg body weight, is the usual baseline requirement.[14]

Magnesium is not ordinarily provided when parenteral fluid therapy is to be of relatively short duration and patients are not severely debilitated. In debilitated adult patients who are not acutely dehydrated and are not suffering from renal insufficiency, 10 to 15 mEq of magnesium sulfate is indicated in the baseline fluid regimen. Magnesium concentration should not exceed 15 mEq per L.

Solutions containing potassium or magnesium *must not be given rapidly*. Rates of administration should not exceed 10 mEq of potassium or 5 mEq of magnesium per hour in the adult.

In the presence of an overexpanded extracellular fluid space with excess total body sodium, the sodium chloride content of baseline fluids should be reduced or eliminated. In the presence of acute or chronic renal insufficiency or severe acidosis with elevation of the plasma potassium level, potassium should not be administered.

The remaining water requirements beyond that used to dissolve the electrolytes suggested are made up by the use of 5 or 10 per cent glucose in distilled water.

Glucose should not be administered at a rate in excess of 0.5 gm per kg per hour to avoid hyperglycemia and possible glycosuria with dehydration. Three hours at a minimum are required for a liter of 5 per cent dextrose. Usual infusion rates are 100 to 200 ml per hour.

It is unphysiologic to provide 2500 ml of fluid containing 125 gm of glucose, 4.5 gm of sodium chloride, and 3.0 gm of potassium chloride in an infusion beginning at seven in the morning and completed by noon, and then to expect the patient to coast the remaining 19 hours of the day. By evening the patient will have disposed of most of the excess water load and will have used up most of the glucose. By midnight the patient will be dehydrated, and starvation acidosis will be developing in most instances. Two infusions spaced about 12 hours apart are required for the average adult. Three or four or even five infusions are required for small children and infants. Often it is simpler to insert a small plastic catheter into a vein and to use this either for continuous slow infusion or for repeated infusions, avoiding the necessity of frequent placement of needles. A dilute solution of heparin in saline solution instilled in such a catheter will often prevent clotting between infusions. However, intravenous catheters or continuously indwelling needles present a severe infection hazard. Catheters should be inserted only with full sterile sugical precautions and should not be left in place for more than 72 hours in most cases.

Vitamins

VITAMIN C. Vitamin C is essential for the healing of surgical wounds. Most surgical patients enter their experience with a good reserve store; however, vitamin C is inexpensive, nontoxic, and fairly easily administered parenterally. A baseline intake of 200 mg per day will assure that the patient does not become depleted.

VITAMINS OF THE B COMPLEX. These vitamins are involved in oxidation of glucose and are also involved in wound healing. Patients likely to have vitamin B deficiency include the elderly and those with gastrointestinal disease, gastrointestinal tract carcinoma, and chronic diseases of the liver, particularly cirrhosis and chronic alcoholism. Vitamin B complex is easily provided parenterally.

VITAMIN K. Vitamin K is usually provided by intramuscular injection except in emergencies, when vitamin K_1 oxide can be used intravenously. It is important in patients with jaundice and those on broad-spectrum antibiotic therapy, particularly if administered orally.

Nutritional Considerations

Baseline requirements of the adult for carbohydrate are met by the administration of 1.5 to 2 gm of glucose per kg body weight per day. One hundred to 150 gm of glucose a day will reduce the demand for amino acids mobilized from skeletal muscle for gluconeogenesis in starvation by about one half. This is a significant saving. In surgical patients undergoing moderately stressful operations who are unable to eat for a few days to a week or so, and are well nourished with normal skeletal muscle mass preoperatively, this is probably all the nutritional support that is required.

However, in patients who are debilitated by chronic illness, or have suffered loss of 10 per cent of body weight or more in the immediate past, and in those suffering from major trauma, sepsis, or burns or having surgery that will result in gastrointestinal dysfunction for a prolonged period, a nutritional regimen must be carefully planned to provide the energy requirements of the patient until he is able to eat, digest, and absorb enough normal foods to survive and convalesce. Total parenteral nutrition (intravenous hyperalimentation) and defined formula diets (elemental diets) both play a significant and vital role in accomplishing these objectives. Details of methodology are widely available and should be consulted.[8, 9*] Important to this discussion is that water and electrolyte requirements and acid-base abnormalities must receive constant attention, and nutritional formulas must be adjusted in volume and content to maintain fluid-electrolyte and acid-base balance. *Assuming that all is well* once a patient is on 2 or 3 liters a day of a standard high caloric intravenous preparation, or on an equivalent amount of a defined formula diet *can be extremely dangerous. Constant supervision of water and electrolyte status is essential.*

Abnormal Losses

This is the second major category for consideration in determining fluid and electrolyte requirements. It includes both external abnormal losses of water, electrolytes, and plasma protein, and internal fluid shifts with functional loss of fluids by sequestration within the body.

External abnormal loss may be in the form of excessive loss of water and electrolytes by normal routes of excretion or secretion, or losses may occur from intraluminal tubes, drains, fistulae, or wounds. The most common of the sources of external abnormal losses in surgical patients is the gastrointestinal tract; next in frequency are losses from surgical wounds, increased evaporation from the skin and respiratory tract, and burns. Sequestration of extracellular fluids into areas of traumatized or infected tissue produces a decrease in the usual distribution of extracellular fluid without external loss or change in body weight.

*See also the article by Blackburn in this symposium (Part II).

Losses From the Gastrointestinal Tract

The normal daily volume of secretions into the gastrointestinal tract is not precisely known but has been estimated to be 8000 to 10,000 ml, of which saliva constitutes 1 to 2 liters; gastric juice, including both acid and mucoid secretions, about 2500 ml; bile, 500 to 750 ml; and pancreatic juice, more than 1000 ml. In addition, secretion of the upper small bowel contributes between 2000 and 3000 ml. All but 100 to 200 ml is normally reabsorbed by the small bowel and the colon.

Abnormal losses from the gastrointestinal tract include water and electrolytes, and varying amounts of protein. The electrolyte content of fluid from the gastrointestinal tract varies significantly with the level from which the bulk of the fluid is derived. Table 9 shows the average and the range of variation of sodium, potassium, chloride, and bicarbonate in fluid from different levels of the intestine in patients with a variety of causes for drainage. It is important to note that of all the secretions of the gastrointestinal tract only bile and pancreatic juice are approximately isotonic in their observed electrolyte content. The average calculated osmolarity of saliva is about 160 mOsm; of fasting gastric juice, in patients without duodenal ulcer, about 180 mOsm; of upper small bowel content, 220 mOsm; and of fluid from the distal ileum, about 240 mOsm. Other substances including mucoproteins, other polysaccharides, urea, and calcium and phosphate, increase the total osmolality beyond these approximations.

The average values shown may be used for semiquantitative replacement of gastrointestinal tract losses. When volumes exceed 2000 ml in 24 hours or when substantial losses (1 liter or more per day) continue for more than a few days, it is wise to send an aliquot of the 24 hour drainage to the laboratory for analysis for electrolytes and protein and to determine the pH of a freshly obtained specimen. With this information more precise replacement can be made.

It is important to note that replacement of abnormal losses is *in addition to* baseline requirements.

Table 9. *Electrolyte Concentration of Gastrointestinal Secretions*

SOURCE OF FLUID	NA, mEq PER L	K, mEq PER L	Cl, mEq PER L	EFFECTIVE HCO_3 mEq PER L
Saliva, average of 3 pt (based on 1 ml/minute)	60	20	16	50
Gastric, average	59	9.3	89	0–1
Range	30–90	4.3–12	52–155	
Upper small bowel, average	105	5.1	99	≅10
Range	72–128	3.5–6.8	69–127	
Ileum, average	117	5.0	106	15–20
Range	91–140	3.0–7.5	82–125	
Bile, average	145	5.2	100	≅50
Range	134–156	3.9–6.3	83–110	
Pancreatic fistula, average of 3 pt	141.6	4.6	76.6	≅70

Internal Fluid Shifts

If the intracellular and extracellular fluid spaces are considered as the two major body fluid compartments, an abnormal "third" fluid space is created when interstitial fluid, plasma, and sometimes red blood cells are sequestered in abnormal amounts in an area of tissue injury. This sequestered fluid is in continuity with the remaining extracellular fluid from which it was derived, yet is unavailable for restoring diminished interstitial fluid and plasma volumes. It is apparent as edema in patients with burns; it also occurs in crush injuries, in peritonitis, in pulmonary infection, in soft tissue and wound infection, and in areas distal to obstructed venous flow. Sequestered fluid is accumulated to some degree postoperatively in all surgical wounds and is substantial in retroperitoneal dissection or with visceral or muscle trauma.

A special type of internal fluid shift is seen with the development of transcellular pooling such as occurs within the gastrointestinal tract with intestinal obstruction or adynamic ileus; the volume of fluid involved may be quite large. These collections of transcellular fluid may become abnormal external losses if they are vomited or drained by intestinal intubation, or they may resolve by reabsorption as the patient recovers gastrointestinal function.

If the volume of sequestered fluid is significantly large, it must be replaced exactly as if an external loss had occurred. Isotonic electrolyte solutions such as Ringer's lactate *without glucose*, and serum albumin fractions are given in sufficient volume and rate to support the circulation and provide adequate urine output.

The major difference between development of a third space of sequestered fluid and an abnormal external fluid loss is that sequestered fluid remains within the body, so that there is no loss of weight. A *gain* in weight results from the necessary replacement of diminished plasma and interstitial fluid volumes of the rest of the body. Also, unlike an external loss, the sequestered fluid will eventually return to the circulation as normal capillary function returns to the affected area—presenting a potential problem in water and electrolyte overloading. Figure 6 illustrates the sequential stages of formation of a third space of injury or sepsis, the result of parenteral fluid therapy, and the phase of resolution of the third space with autoinfusion of ECF water and electrolytes, and diuresis.

Deficits or Excesses

The administration of water, electrolytes, calories, and vitamins as baseline therapy, for replacement of abnormal external losses and for provision of internal fluid shifts is intended to help the patient to maintain normal functional volumes of body fluids, normal concentrations of electrolytes, and a normal pH of plasma and interstitial fluid. However, patients may have deficits or excesses of some or all of the component body fluids at the time when they are first seen and treatment is begun. In other patients significant abnormalities of volume, concentration, and pH may

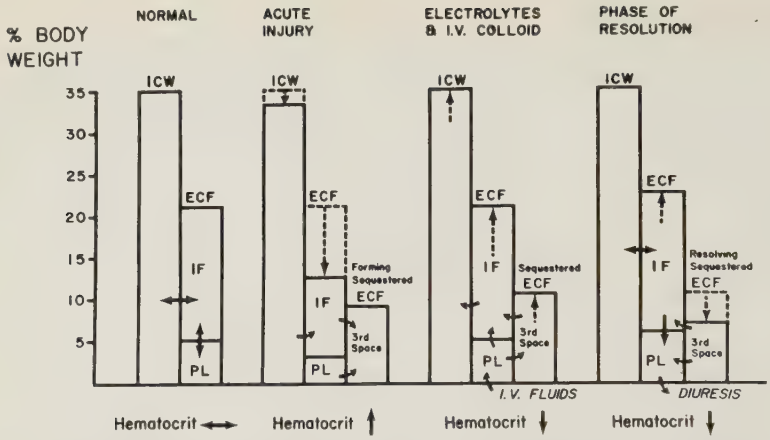

Figure 6. Formation and resolution of sequestered third space fluid. *ICW*, intracellular water; *ECF*, extracellular fluid; *PL*, plasma; *IF*, interstitial fluid, shown as percentage of body weight. Normal status is shown in the first figure. In the second figure, an area of sequestered fluid, in continuity with ECF and plasma, but not available to these normal spaces, is shown forming at the expense largely of plasma and interstitial fluid (IF). Treatment with water, electrolytes and colloid, third figure, results in restoration of ECF, both IF and plasma volumes. When the third space of sequestered fluid begins to resolve, plasma and ICF volumes are further expanded. Diuresis normally results to restore normal volumes.

develop while the patient is under treatment. The replacement of deficits of water and electrolytes necessary to restore function when losses have occurred and the recognition and treatment of excessive fluid volumes or concentrations of electrolytes when present constitute the third major category for clinical consideration in fluid and electrolyte therapy.

Acute Dehydration

Acute change in the volume of total body water can occur either as the result of dehydration or through retention of an excessive amount of water, usually parenterally administered. There is, of course, a comparable change in body weights which, if known, greatly assists in diagnosis. Rapid weight loss due to dehydration is almost entirely extracellular fluid. A loss of 2 per cent of body weight will produce thirst and some oliguria. A loss of 4 per cent of body weight (20 per cent of extracellular fluid) causes oliguria, tachycardia, and often postural hypotension, and an acute extracellular fluid loss of 6 per cent of body weight is a life-threatening event, reducing interstitial fluid and plasma volumes by about 30 per cent and compromising both blood pressure and renal function.

TREATMENT. Replacement of acute loss of extracellular fluid or its functional loss by sequestration or transcellular pooling is best accomplished by infusion of water containing the electrolytes of extracellular fluid. Balanced salt solutions such as Ringer's lactate or a solution of 2 parts of 0.9 per cent sodium chloride and 1 part M/6 sodium bicarbonate are most effective. The rate of replacement can and usually should be rapid when the loss has occurred rapidly. If the loss causing the dehydration has been from vomiting, with an excess loss of hydrogen ion as hydrochloric acid, the plasma carbon dioxide content and pH will be

elevated. Under these conditions the ideal fluid for rapid replacement is isotonic (0.9 per cent) sodium chloride. If a severe metabolic acidosis is present, with a low pH and carbon dioxide content of plasma, initial infusion of 88 mEq of sodium bicarbonate or 500 ml of M/6 sodium lactate solution should precede the use of a balanced salt solution. Close monitoring of serum potassium level is indicated with addition of KCl as indicated to prevent significant hypokalemia as potassium enters the cells with rising pH. *Rapid infusion of glucose-containing solutions should be avoided to prevent a solute diuresis due to glucose overloading.* Glucose solutions should be introduced somewhat later, except in treatment of diabetic ketoacidosis where some glucose will be required as administered insulin becomes effective.

Chronic Dehydration

A patient who has become chronically dehydrated over a period of several days to a week or more, as a result of inadequate intake of water and food, may well lose 10 per cent or more of body weight. The loss of body water in such instances is more evenly distributed between intracellular and extracellular fluids. The effects of combined fluid depletion are less severe than those with acute extracellular fluid dehydration; hypotension and hemoconcentration are less marked, and the degree of oliguria is less.

Treatment. Rehydration in such a patient requires replacement of the extracellular fluid deficit in sufficient volume to raise urine volume to 25 to 50 ml per hour and to reduce the hematocrit to normal levels. A period of days rather than hours is desirable for repletion of the intracellular water and potassium deficits. Emergency surgical measures, if required, can be performed after repletion of the extracellular fluid component. Complete rehydration should not result in return to predehydration weight because of the loss of protein and fat during the period of underhydration and semistarvation.

Dehydration by Primary Water Loss: Desiccation

This occurs as the result of excessive loss of water vapor or of very hypotonic solutions with the retention of extracellular fluid electrolytes and an increase in all the solutes of the plasma with a rise in plasma osmolality. The common clinical settings are those of excessive evaporation of water from the skin and respiratory tract, as seen with fever and hyperventilation due to metabolic acidosis. Tracheostomy and the administration of insufficiently humidified oxygen by catheter are additional respiratory causes. A high volume of dilute urine, as seen with diabetes insipidus, use of osmotic diuretics, and excessive sweating, all with inadequate water replacement, produce excessive water loss. The open treatment of burns with massive loss of water vapor from injured skin surfaces is particularly likely to produce desiccation dehydration. Oliguria, azotemia, fever, disorientation, coma, convulsions, and death will follow. Hypotension is usually a late complication.

Laboratory findings in this setting demonstrate an increase in the concentration of all the solutes of plasma, with an increase in osmolality. Serum sodium concentration is the key, and values of 160 mEq per L or

more may be found, denoting osmolality of more than 325 mOsm. The hematocrit will rise in proportion to loss of total body water when the process takes days to develop as is usually the case; therefore it will not be as high as with acute extracellular fluid loss. Urine is highly concentrated and small in volume.

TREATMENT. Treatment consists of the administration of water as 5 per cent glucose solution intravenously, or water by mouth or into the stomach or small bowel in sufficient volumes to restore electrolyte concentrations and urine volume to normal. The rate of administration will depend somewhat on the rate at which water was initially lost; the more rapid the loss, the more rapid can be rehydration. Usually 1 or 2 days are required to bring the serum sodium level down to normal. Some salt may be required in the later stages of rehydration if significant amounts have been lost as the process has developed. An estimation of the volume of water required can be made from the loss of total body water necessary to raise the hematocrit and serum sodium to the levels observed.

Chronic Overexpansion of Extracellular Fluid

With chronic illnesses such as cancer, liver disease, chronic infection, starvation, or cardiac decompensation, the patient often will present with an overexpansion of the extracellular fluid space with an excess of total body sodium despite hyponatremia. Such a patient will have a decrease in the normal intracellular water because of a diminished relative volume of body cell mass. With the characteristic fall in body cell mass, as per cent of weight, there is a relative expansion of the extracellular fluid space. Such patients are usually hyponatremic, with serum sodium concentrations in the low 130 mEq range. Usually total body potassium is markedly depleted although the plasma concentrations of potassium may be normal or even a little high. In addition there is usually a considerable hypoproteinemia and a reduction in the normal osmolality of the plasma with the osmolality in the range of 260 to 270 mOsm.

Water and sodium retention are exaggerated postoperatively in such patients, and more marked hyponatremia and hyperkalemia often occur. They have a very poor tolerance for the administration of large volumes of extracellular fluid expander such as Ringer's lactate solution or saline solution. They also tolerate free water, as glucose in water, poorly, holding on to excessive water intake with further dilution. The expanded extracellular fluid space with hyponatremia is the most common pattern of water and electrolyte abnormality seen in surgical patients and is one of the most difficult to treat once it becomes established.

TREATMENT. Treatment of this dilutional hyponatremia must not be by the administration of salt solutions on some formula based on unit deficit multiplied by a theoretical volume for extracellular fluid; rather it must be based on a combination of a restriction of water intake to less than that required by the normally hydrated individual and the restoration of the red cell mass and plasma volume to normal by the transfusion of blood or the infusion of plasma, or both. Since a large intracellular potassium deficit is usually present in such patients, the electrolyte need is usually for potassium rather than for sodium.

Hypertonicity Due to Solute Loading

This is usually the result of inadequate intake of water in patients who are receiving tube feedings of mixtures which are high in protein and salt in relation to water content. The syndrome is likely to develop in patients who have had head and neck surgical treatment, those on gastrostomy feedings, unconscious patients being tube-fed, and patients with brain stem injury. Hypertonicity due to solute loading can result from the exclusive use of an isotonic balanced salt solution such as Ringer's lactate solution given with the mistaken idea that such a solution will meet baseline requirements for patients on parenteral fluids. Unless renal function permits excretion of urine of very high specific gravity with elimination of excessive electrolyte, urea and other solutes in a volume of water smaller than that administered, both hypernatremia and azotemia will result.

Laboratory findings demonstrate an increased concentration of all plasma solutes, both electrolytes and crystalloids, which is out of proportion to changes in hematocrit. An elevated plasma sodium level in the presence of a moderate to large urine output is the key to diagnosis differentiating these patients from those with desiccation dehydration. The serum sodium may reach levels of 170 mEq per L or more in severe cases.

Treatment. This consists of the administration of large volumes of water orally or via a tube, or parenterally as 5 per cent glucose in water, while at the same time eliminating, or at least reducing, the osmolar load. Caution must be exercised in order to reduce the osmolality relatively slowly. The entire body, including the cerebrospinal fluid and brain, becomes hypertonic during the solute loading period; cerebral edema, convulsions or coma may result if the extracellular fluid osmolality is reduced too rapidly. Large volumes of urine will persist for several days during solute release, and the hematocrit will not change greatly unless dehydration has also been present in significant degree.

Overhydration, Hypotonicity, and Water Intoxication

The opposite of solute overloading occurs with the excessive administration of water in the presence of antidiuresis. This condition exists in a chronic state in patients with wasting illnesses but may be seen acutely usually because of excessive and ill-advised parenteral administration of glucose and water.

Patients with cancer, heart disease, liver disease, renal insufficiency, or chronic infection are likely to have an expanded extracellular fluid before surgical treatment. They are particularly prone, as previously noted, to retain water and electrolytes and further to expand and dilute extracellular fluid.

Water intoxication is an acute form of hypotonic dilution. Drowsiness, weakness, and a fall in urine volume are early symptoms, followed by convulsions and coma. A rapid weight gain will always occur. Peripheral and pulmonary edema may appear but are not always present. Water intoxication may result from excessive administration of parenteral glucose and water, from absorption of water from the colon as the result of enemas or colon irrigations given for distention, or from water absorption

from wounds and burns treated with hypotonic wet dressings. Water intoxication is a particular hazard of the dilute silver nitrate treatment of burns. It is particularly likely to occur in patients with inappropriate antidiuretic hormone release. (See previous sections on body water and ADH.)

Laboratory findings include a low concentration of serum sodium, usually less than 120 mEq and often less than 110 mEq per L. The urine may contain a substantial concentration of sodium, 30 mEq per L or more despite the extremely low plasma value, due to an inappropriate sodium release in the presence of a very large extracellular fluid volume. Adrenal insufficiency and primary renal tubular disease must be excluded. The rapidity of fall of the plasma sodium concentration is apparently of greater significance than the absolute values. Cerebral edema from a shift of water into the cerebrospinal fluid due to the difference in osmolality is the probable cause of convulsions and coma.

TREATMENT. Either total water restriction for a time or the very slow administration of a small volume of water as hypertonic glucose (20 per cent)—not more than 500 ml over 24 hours—is required. If the patient has good cardiovascular function and central venous pressure is within normal limits, small volumes (300 ml or less) of hypertonic sodium chloride solution (5 per cent) should be given slowly with monitoring of central venous pressure. This will begin restoration of extracellular fluid osmotic pressure and promote renal excretion of water. No attempt should be made to administer salt with a "formula" based on extracellular fluid deficit for severe overloading can result. Time and patience will result in a rising urine volume and an increase in serum sodium concentration with recovery in most cases. In an emergency, hemodialysis with ultrafiltration to remove water may be desirable.

SUMMARY OF CLINICAL APPLICATION: FLUID AND ELECTROLYTE BALANCE

Fluid and electrolyte requirements of surgical patients may be considered in three categories:

1. *Baseline Requirements.* The amount of water, sodium, potassium, and chloride required to meet normal requirements of a patient deprived of oral intake. Also, minimal carbohydrate requirements to reduce protein catabolism in starvation.

2. *Abnormal Losses.* The semiquantitative replacement with respect to volume and electrolyte content of losses from the gastrointestinal tract, and wounds. Also provision for the formation of a third space of sequestered extracellular fluid, and sometimes blood, in areas of trauma, sepsis, and burns, using volumes sufficient to restore or maintain cardiovascular and renal function.

3. *Deficit.* Estimation of and provision for water and electrolyte needs in dehydration, together with *restriction* of water and sodium intake in patients with overexpansion of extracellular fluid.

The daily needs of patients is the algebraic sum of the three categories in water volume and in electrolyte content of administered fluids.

ACID-BASE BALANCE

L. J. Henderson in 1909 pointed out the significance of bicarbonate as a reserve of alkali in excess of acids other than carbonic, and developed the "Henderson equation." Hasselbalch devised a hydrogen electrode which would function in the presence of carbon dioxide, demonstrated the influence of respiration on blood pH, and suggested the logarithmic form of Henderson's equation, now known as the Henderson-Hasselbalch equation (vide infra). D. D. Van Slyke, who recounted these facts in *Summary of Acid Base History in Physiology and Medicine*,[33] developed volumetric apparatus for measuring the total CO_2 content of plasma, and demonstrated that the Gibbs-Donnan theory, as applied to the distribution of electrolytes across membranes, fitted chloride and bicarbonate distribution with oxidation and reduction of hemoglobin in the erythrocyte-plasma system. He also defined buffers as "substances which by their presence in a solution increase the amount of acid or alkali that must be added to cause a unit change in pH." Peters and Van Slyke in 1931 introduced the terms metabolic acidosis and alkalosis and respiratory acidosis and alkalosis referring to those conditions in the body which produced changes primarily in the plasma bicarbonate concentration as metabolic and to those primarily affecting CO_2 tension as respiratory.[21]

This physiologic language has persisted in clinical medical practice where acidosis and alkalosis are defined as abnormal conditions caused by the accumulation or loss of acid or base.

With rapidly increasing use of pH determination of the blood by clinicians and clinical laboratories in recent years, greater emphasis is being placed on the state of the blood in which pH deviates from normal. In this *laboratory* language, acidosis and alkalosis are defined in terms of change in pH of the blood, and as changes in whole blood buffering systems in terms of base excess, or negative base excess, depending upon the amount of strong acid or strong alkali necessary to return a sample of blood to normal pH under standard conditions of temperature, O_2 saturation, and Pco_2.

Definitions of Acid-Base

Because of the differences in physiologic (clinical) and laboratory terminology in definition of acidosis and alkalosis and the confusion that resulted, an international conference was held in 1966 to attempt to develop common definitions. The following definitions are those agreed upon by an ad hoc committee of the conference and are used in the clinical discussion which follows.

For more detailed information, the minutes of the Conference on Acid Base Measurement should be consulted.[7]

Acid-Base Terminology. The Bronsted-Lowery System: An acid is a substance which is a proton donor. A base is a substance which is a proton recipient. The general form for acid-base relationship is given as:

$$A_1 + B_2 \rightleftarrows A_2 + B_1$$

where A_1, B_1 represent one conjugate acidbase pair and A_2, B_2 represent a second conjugate acid-base pair. This takes into consideration the active role of water in solutions.

$$A_1 + B_2 \rightleftarrows A_2 + B_1$$
$$CH_3COOH + H_2O \rightleftarrows [H_3O^+] + [CH_3COO^-]$$
$$H_2CO_3 + H_2O \rightleftarrows [H_3O^+] + [HCO_3^-]$$

Water and H_3O^+ represent one conjugate pair in both systems, acetic acid and the acetate ion, and carbonic acid and bicarbonate ion the second conjugate pairs, respectively.

BUFFERS. Under Van Slyke's definition of buffers, carbonic, phosphoric, and organic acids and the acidic portions of protein molecules (proton donor sites), together with their conjugate bases, are buffers. Sodium, potassium, magnesium, calcium, and chloride ions as such do not function as buffers and are neither acids nor bases. They are "aprotes" since they neither donate nor receive protons.

pH—HYDROGEN ION CONCENTRATION AND ACTIVITY. pH is the logarithm of the reciprocal of the hydrogen ion concentration:

$$pH = \log \frac{1}{[^aH^+]}$$

In thermodynamic terms, pH defines the hydrogen ion activity:

$$pH = \log 1 = -\log {}^aH^+$$

Since the activity coefficient for hydrogen ion is not precisely known, it is assumed to be 1, therefore:

$$aH^+ = cH^+$$

where cH is hydrogen ion concentration expressed as nanomoles per L (10^{-9} moles). At pH values of whole blood compatible with survival, the concentration of hydrogen ion at 37°C is:

pH	*cH(nanomoles/L)*
7.0	100
7.1	80
7.2	63
7.3	50
7.4	40
7.5	32
7.6	25
7.7	20

It is essential that the temperature and whether whole blood or plasma is examined be stated in reporting both pH and hydrogen ion content or activity.

The Carbon Dioxide System. Total Carbon Dioxide Concentration (T_{CO_2}). The total carbon dioxide extractable from a biologic fluid with strong acid. This includes dissolved carbon dioxide, carbonic acid, bicarbonate ion, and carbamino compounds. This is the usual value reported by clinical laboratories as total CO_2 or CO_2 content of plasma.

Partial Pressure of Carbon Dioxide, or Carbon Dioxide Tension (P_{CO_2}). The partial pressure of carbon dioxide in gas phase in equilibrium with a biologic fluid is usually reported in mm Hg. While P_{CO_2} can be directly measured by diffusion through a specially prepared Teflon membrane standardized with gas of known CO_2 concentration, the value is often calculated from pH and T_{CO_2} by use of a nomogram based on the Henderson-Hasselbalch equation.

Carbonic Acid Concentration ($HHCO_3$). In biologic fluids, this quantity is very small in comparison to dissolved carbon dioxide concentration. The usual units are mM per L or mEq per L.

Dissolved Carbon Dioxide Concentration. Strictly speaking, this is the quantity of dissolved carbon dioxide gas in a specified volume; usually $HHCO_3$ is included. The sum of the two is designated as $S \times P_{CO_2}$ where S is the solubility coefficient relating the sum of the concentrations of dissolved CO_2 and H_2CO_3 in mM per L to P_{CO_2} in mm Hg. This value is temperature dependent; at 37°C for blood or plasma, S = 0.0306.

Bicarbonate Ion Concentration (HCO_3^-). The chemical definition is the concentration of HCO_3^- in biologic fluids. However, in physiologic studies and clinical use, it is calculated as total $CO_2 - S \times P_{CO_2}$. This value includes carbamino compounds and carbonate ion in addition to bicarbonate ion, which makes very little difference in plasma or interstitial fluid, but introduces large errors for intracellular fluid:

$$[HCO_3^-] = TCO_2 - S \times P_{CO_2}$$

Standard Bicarbonate Concentration. The plasma bicarbonate ion concentration of plasma equilibrated at P_{CO_2} of 40 mm Hg and 37°C. Units are mEq per L.

Bicarbonate Concentration at Standard pH. This is similar to standard bicarbonate concentration except that pH is set at 7.40 and P_{CO_2} is the variable. Units are mEq per L.

Carbon Dioxide Combining Power. The total carbon dioxide concentration of plasma, anaerobically drawn and separated from blood, and equilibrated to P_{CO_2} of 40 mm Hg at room temperature. Units are mM per L. This value is rarely used because of dependence on conditions in the blood when the plasma is separated, and because it is dependent on uncontrolled room temperature.

Buffer Base. The sum of the concentration of buffer ions of whole blood bicarbonate, plasma proteins, and hemoglobin. Units are mEq per L. This value and base excess, which is derived from it, are determined on whole blood, and are hemoglobin dependent.

Base Excess. As defined by Astrup and Siggard Anderson:[7, 29] "The base concentration (of whole blood) as measured by titration with strong acid to pH 7.40 at a P_{CO_2} of 40 mm Hg at 37° centigrade. For negative base

excess, the titration must be carried out with strong base." Units are mEq per L. Negative base excess is sometimes termed base deficit.

HENDERSON-HASSELBALCH EQUATION. The older presentation of this equation for plasma is:

$$pH = pK_i + \log_{10} \frac{BHCO_3}{HHCO_3} \left(\frac{20}{1} \text{ at pH } 7.40 \right)$$

where $BHCO_3$ is bicarbonate associated with base (largely Na) and $HHCO_3$ is CO_2 in solution. pK_i is 6.1 for $HHCO_3$. Since $HHCO_3$ is a function of Pco_2, the equation is now expressed as:

$$pH = pK_i + \log \frac{[\text{total } CO_2 - S \times Pco_2]}{[S \times Pco_2]}$$

$$pH = pK_i + \log \frac{[HCO_3^-]}{[S \times Pco_2]} \text{ where } pK_i = 6.11$$

where $(S \times Pco_2)$ is the partial pressure of Co_2 in mm Hg multiplied by the solubility coefficient of CO_2 and $HHCO_3$. S = 0.0306 at 37°C.

The Henderson-Hasselbalch equation is for serum or plasma. Calculation of one value (usually Pco_2) from the other two is frequently done in clinical laboratories.

Acid-Base Status of the Blood: Definitions for Clinical Evaluation and Treatment

Two methods of reporting and evaluating the acid-base status of whole blood and plasma are in current use. Both have strong advocates and each method has both advantages and disadvantages.

THE CO_2-BICARBONATE BUFFER SYSTEM METHOD. The older and more commonly used method in the United States characterizes the acid-base status of the blood (and by inference, of the patient) in terms of the CO_2-bicarbonate buffer system *of the plasma*. Clinically the most useful measurements are: plasma bicarbonate (HCO_3^-); blood or plasma Pco_2; and plasma pH. Plasma bicarbonate is determined from total CO_2 content of plasma and the pH, from the Henderson-Hasselbalch equation. Pco_2 is either directly measured with one of several instruments that depend on diffusion of CO_2 through a special CO_2 membrane or it is calculated from total CO_2 and pH. Plasma pH is measured directly from plasma protected against CO_2 loss to air, using a glass electrode pH meter which is standardized against precisely prepared buffer solutions of known pH. The measurement is made at 37°C.

Plasma bicarbonate concentration is used as a measure of the metabolic component of acid-base abnormalities, recognizing that alterations in plasma bicarbonate concentration may be manifestations of a primary metabolic derangement or may reflect compensatory changes secondary to a respiratory Pco_2 derangement. Similarly, Pco_2 is regarded

as a measure of the respiratory component of acid-base disequilibria, recognizing that such changes may represent either the primary derangement, or be due to secondary compensatory changes.

THE WHOLE BLOOD BASE EXCESS, OR Δ BUFFER BASE METHOD. Proponents of this system, based on the work of Siggard Anderson and Astrup[7, 29] hold that the metabolic component of acid-base equilibrium can be most precisely determined by titrating to pH 7.40 with strong acid the base excess of whole blood which is equilibrated at P_{CO_2} at 40 mm Hg at 37°C. The determination of the number of mEq of base lost or gained by 1 liter of whole blood under these circumstances is independent of respiratory function and represents nonvolatile acid or base accumulation. It is stated that the two most valuable parameters for clinical evaluation of acid-base metabolism are P_{CO_2} and the accumulation of nonvolatile acids or bases.

Values that are determined include whole blood base excess or ΔBb, blood or plasma P_{CO_2}, and plasma pH.

Base excess is not independent of P_{CO_2} in vivo. The titration curve of blood in vivo is slightly different than in vitro. As with any system of analysis of acid-base status, a careful assessment of the patient is essential for clinical interpretation and for determination of therapy.

In the discussion which follows, the first of the two methods will be used. Interconversion is possible with a graph, if both oxygen saturation and hemoglobin concentration of whole blood are known, as is often the case with seriously ill patients. Regardless of which method of acid-base terminology and analysis is used, it must be remembered that there are very few independent acid-base variables in blood; total CO_2, (HCO_3^-), (H^+), (OH^-) and (hemoglobin$^-$) are dependent variables. Stewart[30] has proposed that there are only three independent variables in acid-base regulation: (1) The partial pressure of CO_2, P_{CO_2}, which is under respiratory control. (2) The difference between the sum of the inorganic cations (excluding H^+) and the anions of strong acids, i.e., $(Na^+ + K^+ + Mg^{++} + Ca^{++}) - (Cl^- + HPO_4^= + SO_4)$. This component is under renal control through renal regulation of both cation and anion concentrations. (3) The total buffer present per liter, including protein, and hemoglobin in the case of blood. With knowledge of these three independent variables, the concentration of all the dependent variables, including pH and (HCO_3^-) can be calculated from computer-derived nomograms.

CAUSES OF ACID-BASE IMBALANCE. There are two main causes of acid-base disturbance, respiratory, due to abnormalities of CO_2 excretion, and metabolic, due to abnormalities of production, ingestion, or excretion of hydrogen ion.[7] Disturbances in one of the two categories usually provoke compensation by the other system. Most patients have a primary defect in one system, with a secondary compensating change in the other. However 41 per cent of 139 patients studied in detail by Elkinton had mixed primary types of derangements due to a wide variety of diseases.[10]

Acidosis and alkalosis should be referred to as conditions which would result in alteration of the pH of blood and plasma, if there were no secondary compensating changes and may result in pH changes even with compensation. Acidosis or alkalosis can be further defined as respiratory,

metabolic, or mixed as the laboratory findings and the clinical pattern indicate. More specific descriptive adjectives, such as renal, diabetic, lactic, or respiratory, can be used, without necessarily indicating a change in pH per se.

The Ad Hoc Committee on Acid Base Terminology[7] strongly advised that secondary compensatory mechanisms are not and should not be considered as acidosis or alkalosis. Rather the primary etiologic factor should be described, and compensation indicated, such as "metabolic acidosis with compensatory fall in Pco_2" or better still, simply give the laboratory numbers as observed.

Mixed disturbances exist when there are two or more distinct etiologic factors present. These should be described clearly to differentiate them from a single factor with compenstion, e.g., "mixed disturbance—metabolic acidosis and respiratory alkalosis," or "mixed disturbance—diabetic and renal acidosis."

Table 10 gives the range of normal values found for the set of determinations commonly used in acid-base evaluation. A Siggard-Anderson nomogram (Radiometer A/S, Copenhagen, Denmark) is used in determining buffer base and base excess after equilibrating arterial blood (90 per cent saturated with oxygen or more) at 37°C at two standard Pco_2 values, one higher and one lower than Pco_2 40 mm Hg. Hemoglobin concentration must be considered.

A wide variety of nomograms relating pH, total CO_2, and Pco_2 are in use today. One variant (Fig. 7) developed by R. V. Stephens in our laboratory from the nomogram devised by Poppell[23] has proved useful clinically because it relates the two most commonly measured plasma factors in acid-base determination, pH and total CO_2, to acidosis and alkalosis of both metabolic and respiratory origin. The pH is plotted in such a fashion that Pco_2 values are straight lines, thus making determination simpler.[24]

Figure 8 summarizes the primary changes that occur in pH, Pco_2 and total CO_2 in metabolic and respiratory acidosis and alkalosis, together with the early compensatory changes that are induced by the primary condition.

Table 10. *Whole Blood and Plasma Values for Acid-Base Evaluation**

	RANGE OF NORMAL	95 PER CENT CONFIDENCE LIMITS OF LABORATORY METHOD
Hemoglobin	12.5–16.0 gm per cent	± 5 per cent of value
pH (arterial)	7.35–7.45	± 0.02 pH units
Pco_2 (arterial)	35–45 mm Hg	± 3 per cent of value
Plasma total CO_2	24–28.8 mmol per L	± 0.2 mmol per L
$[HCO_3^-]$ plasma	22.85–27.45 mEq per L	Calculated value
Buffer base	43–47 mEq per L whole blood	
Base excess	−3 to +3 mEq per L	Calculated value

*From Randall, H. T.: Water, electrolyte, and acid-base balance. *In* Goodhart, R. S., and Shils, M. E. (eds.): Modern Nutrition in Health and Disease, 5th ed. Philadelphia, Lea and Febiger, 1973. Used with permission.

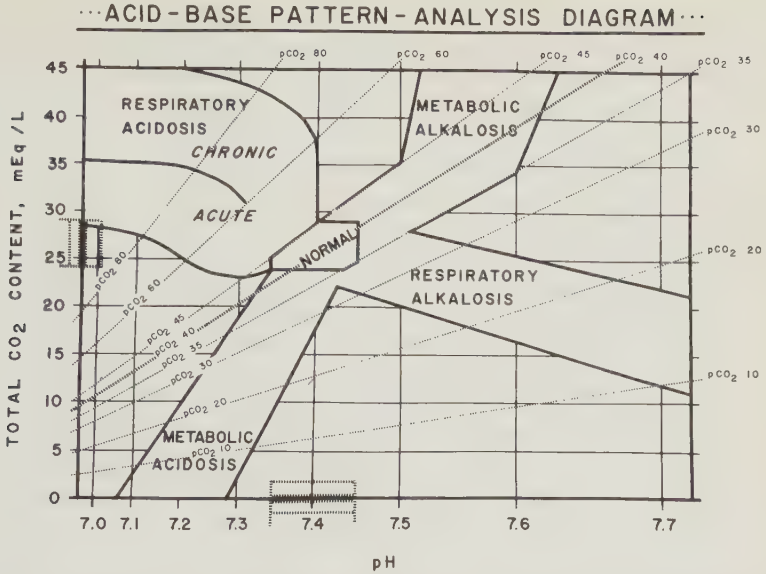

Figure 7. Nomogram by R. V. Stephens relating total carbon dioxide content (Tco_2) and pH of plasma to alterations in acid-base balance. Method of plotting pH results in Pco_2 isobars being straight lines. The areas within the zones marked metabolic acidosis and metabolic alkalosis, and respiratory acidosis and alkalosis encompass the usual four primary acid-base derangements with secondary compensatory changes. The increase in Pco_2 which is compensatory for metabolic alkalosis is limited by oxygen demand, and is usually seen when Tco_2 is greater than 35 mEq per L. Acute respiratory acidosis results in minimal change in Tco_2, in contrast to chronic respiratory acidosis. When more than one distinct etiologic factor is present, for example, metabolic acidosis and respiratory alkalosis, the plot of pH and Tco_2 will tend to fall between the areas indicating each single factor and its compensation.

Nomograms of various types are helpful in determining clinical acid-base status, but must not be considered diagnostic in themselves.

ALTERATIONS IN PH, Pco_2 AND TOTAL Co_2 IN ACIDOSIS AND ALKALOSIS

STATE	Δ pH	Δ Pco_2	Δ Tco_2	EARLY SECONDARY COMPENSATION
Metabolic Alkalosis	↑	± TO ↑	↑ *	Variable Δ Pco_2 within O_2 limits. Renal excretion $[HCO_3]$
Respiratory Alkalosis	↑	↓ *	± TO ↓	Renal ? $[HCO_3]$ excretion ↑ Organic acid & Hypoxia
Metabolic Acidosis	↓	↓	↓ *	Hyperventilation. Renal $[H]$ excretion
Respiratory Acidosis	↓	↑ *	↑	Renal excretion of Cl and $[H]$

* INITIAL AND PRIMARY CHANGE

Figure 8. The primary changes in pH, Pco_2 and Tco_2 resulting from metabolic alkalosis, respiratory alkalosis, metabolic acidosis, and respiratory acidosis are shown and marked with an asterisk. Compensatory changes are indicated. These tend to reduce the effect of the primary change on pH.

METABOLIC ACIDOSIS. Metabolic acidosis is a set of conditions that without compensatory changes would tend toward a decrease in the pH of blood.

Usually compensation is incomplete. The pH of arterial blood is less than 7.38, total CO_2 less than 24 mEq and Pco_2 less than 35 mm Hg. The common causes of metabolic acidosis may be divided into four major groups.

1. Increased production of organic acids.
   a. Ketosis — with increased fat metabolism. This occurs in diabetes mellitus; starvation; hypermetabolism of thyrotoxicosis, fever and sepsis; high fat–low carbohydrate diets; following trauma and major operations, often combined with relative starvation and acute dehydration, particularly in infants.
   b. Cellular hypoxia including lactic acidosis resulting from prolonged inadequate oxygenation of tissues; pulmonary insufficiency, acute or chronic; hypermetabolism due to exertion, seizures, fever; congestive heart failure; shock, whether due to hemorrhage or sepsis; anesthesia—cardiopulmonary bypass and acute adrenal insufficiency.
2. Decreased excretion of hydrogen ion due to renal dysfunction, with retention of (SO_4^-) and (HPO_4) ions. This occurs with decreased renal blood flow in shock, cardiac failure, hypovolemia, and vascular disease, intrinsic renal disease, acute or chronic; obstructive uropathy; renal disease plus a high protein diet, administration of $MgSO_4$, NH_4Cl, or methionine and ureterosigmoidostomy with renal disease.
3. Loss of base in excess of chloride, phosphate and sulfate ions resulting from dehydration with sodium loss from diarrhea, biliary or pancreatic fistulae, long tube drainage or small bowel fistula and diuretics that inhibit carbonic anhydrase.
4. Increased intake of acid, e.g., acidifying salts such as NH_4Cl and $CaCl_2$; amino acid solutions given parenterally or in elemental diets, particularly if the amino acids are present as hydrochlorides. Sodium chloride in the presence of reduced renal function.

Compensation for metabolic acidosis is both respiratory and renal. Respiration is increased in rate and particularly in depth. Marked and sustained hyperventilation is characteristic of metabolic acidosis and is a very useful clinical sign of its presence.[2]

Treatment of metabolic acidosis is directed toward the cause of acidosis. In addition, therapy must be planned to reinforce the diminished bicarbonate reserve and combat the hyperkalemia, which may become a serious threat. Efforts should be made to keep the CO_2 content of the plasma at or above 15 mEq per L, and the best drug for this purpose is sodium bicarbonate, which provides sodium without the anion of a strong acid. Experience has demonstrated that it takes 2 mEq of $NaHCO_3$ per L of extracellular fluid to raise the plasma CO_2 by 1 mEq per L. Thus, a patient who has a CO_2 content of 10 mEq per L and who weighs 70 kg will require 140 mEq of $NaHCO_3$ to restore the CO_2 to 15 mEq per L ($70 \times 0.2 \times 5 \times 2 = 140$). This may be administered as an isotonic solution (1.2 per cent) or in critically ill patients as a 5 per cent solution given intravenously very slowly. Serum potassium level may fall markedly and, hence, must be carefully monitored. Potassium must be administered if this occurs. It is not necessary to give enough $NaHCO_3$ to bring the plasma CO_2 to normal levels, and the amount of sodium required to do so may be excessive. Titration of the patient to maintain a Tco_2 somewhere above 15 mEq per L is usually adequate in the short-term management of metabolic acidosis.

METABOLIC ALKALOSIS. Metabolic alkalosis is a condition which

would tend to elevate the pH of blood or plasma in the absence of compensatory changes and which does so when compensation is incomplete. The common causes of metabolic alkalosis are a loss of body acid, particularly loss of chloride ion, an excess of base, usually sodium, and the loss of significant amounts of potassium.

1. Loss of acid results from vomiting; gastric intubation with loss of acid gastric secretion; gastrocolic fistula or aciduria with potassium and chloride depletion.
2. Excess of base results from absorbable antiacids — particularly $NaHCO_3$; sodium salts of weak acids, particularly lactate, citrate, blood transfusions with ACD anticoagulant; Ringer's lactate solution to replace acid or neutral losses from the gastrointestinal tract; or with vegetable diets.
3. Potassium depletion results from the use of diuretics, particularly thiazides and furosemide; gastrointestinal losses, particularly lower gastrointestinal tract, diarrhea; prolonged unreplaced loss of chloride ion with alkalosis and enhanced renal secretion of potassium; lack of potassium intake, particularly in intravenous fluids and with vomiting; adrenal steroid administration, or Cushing's disease or potassium-losing renal tubular disease.

Compensation for metabolic alkalosis is also respiratory and renal. In some patients there is diminished ventilation, with some increase in P_{CO_2}, particularly when the CO_2 content of the plasma rises above 35 mEq per L.

Goldring et al.[13] studied normal volunteers made alkalotic under controlled conditions by administration of buffers, diuretics, and aldosterone. Alkalosis induced by sodium bicarbonate, THAM, and ethacrynic acid was associated with high values of arterial P_{CO_2} (P_{CO_2} values of 46 to 48 mm Hg) while alkalosis induced by thiazide diuretics and aldosterone was associated with normal arterial blood P_{CO_2} values despite comparable increase in HCO_3^- values to a range of 30 to 34 mEq per L.

An extreme example of respiratory compensation has been observed in a 49-year-old man with Zollinger-Ellison syndrome, who was placed on nasogastric drainage because of marked vomiting. Losses of 5000 ml a day of gastric juice for 48 hours containing Na^+ 29 mEq per L, K^+ 7.2 mEq per L and Cl^- 148 mEq per L, despite large volumes of parenteral saline, resulted in an arterial pH of 7.52, with P_{CO_2} of 73 mm Hg and P_aO_2 163 mm Hg on 40 per cent O_2 by face mask. T_{CO_2} was greater than 45 mEq per L and Cl was 72 mEq per L with sodium 147 mEq per L and K^+ 2.7 mEq per L. Correction with sodium chloride, potassium chloride, and arginine hydrochloride infusions prevented imminent death.

Most seriously ill patients demonstrate relatively small, or no evidence of respiratory compensation for metabolic alkalosis, probably because the hypoventilation necessary is limited by oxygen demand, and further limited if a significant amount of pulmonary arteriovenous shunting is present. Uncompensated alkalosis induces further hypoxia by decreasing oxygen availability to tissues with a left shift in the Bohr curve of oxygen dissociation from hemoglobin.

Initial renal compensation following the loss of chloride ion occurs by excretion of sodium bicarbonate resulting in an alkaline urine. Unless adequate amounts of sodium, potassium, chloride, and water are made available, this soon leads to dehydration. Metabolic alkalosis increases renal excretion of potassium, and as depletion of this ion develops, renal tubular reabsorption of bicarbonate increases, leading to the paradox of an acid urine in an alkalotic patient and helping to perpetuate the alkalosis.

Treatment of Metabolic Alkalosis. Alkalosis caused by sodium retention (steroids or exogenous administration) will correct itself on cessation of therapy and administration of potassium chloride.

Alkalosis resulting from the loss of chloride requires the administration of both sodium and potassium chloride. Chloride can also be administered as the hydrochloride of arginine, and hydrochloric acid, 0.1 normal, has been given mixed with 5 per cent glucose into a large central vein in desperate cases.[1, 26]

RESPIRATORY ACIDOSIS. Retention of carbon dioxide is a condition which, if compensating mechanisms were not available, would produce a fall in the pH of blood. Although complete compensation is seen in mild cases, compensation is usually incomplete, with a fall in pH of the blood, despite a compensatory increase in total CO_2 of the plasma. There is an increase of hydrogen ion and a decrease in pH of the blood caused by an increase in Pco_2 and in H_2CO_3. The pH of blood is usually less than 7.38, and the Pco_2 is more than 47 and usually more than 50 mm Hg. The CO_2 content of the plasma is not altered in the acute phase but rises with compensation and is elevated in the chronic form. Arterial blood gas and pH determinations are diagnostic.

Common causes of respiratory acidosis are: (1) Hypoventilation, which may be due to airway obstruction, pneumothorax, pleural effusion, atelectasis, pneumonitis, thoracotomy, upper abdominal incisions, or skeletal muscle weakness. Carbon dioxide retention often occurs acutely as the result of medications which depress respiration, e.g., anesthesia, narcotics, barbiturates, and other sedatives or muscle relaxants. (2) Arteriovenous shunting in poorly ventilated segments of the lungs due to atelectasis or pneumonitis or interstitial edema, resulting in elevation of systemic arterial Pco_2. (3) Inadequate ventilation with respirators.

Compensation for respiratory acidosis is renal with increased tubular reabsorption of sodium and bicarbonate and increased secretion of chloride and hydrogen ion. The result is a rise in plasma bicarbonate which partially or completely restores pH to normal.

Treatment of Respiratory Acidosis. Acute respiratory acidosis requires emergency treatment, the success of which rests on recognition of inadequate ventilation long prior to the development of cyanosis. Restlessness and a rise in blood pressure and pulse rate may be the first signs of hypercapnea and hypoxia. Hypotension follows. The use of narcotics only increases the problem through suppression of the respiratory center. Making certain of the airway, administering oxygen cautiously, and assisting respiration are indicated.

Chronic respiratory acidosis is a common problem secondary to constrictive pulmonary disease, chronic bronchitis, and emphysema. Such patients are poor surgical risks, and require ventilatory support. Recognition in advance of surgery of the existence of pulmonary insufficiency is essential, and treatment, including cessation of smoking prior to elective surgery and respiratory therapy, is mandatory.

RESPIRATORY ALKALOSIS. Respiratory alkalosis is a primary decrease in Pco_2 and in $HHCO_3$ and is reflected in an increase in pH of the blood. The cause is increased ventilation, in both rate and depth, with a

reduction of the normal alveolar P_{CO_2} below 35 mm Hg. Initially there is no change in the CO_2 content of the plasma.

The causes of hyperventilation and respiratory alkalosis are multiple and include: (1) apprehension and pain; (2) fever, particularly if associated with some lung infection or atelectasis; (3) hepatic failure with elevated blood ammonia; (4) central nervous system injury; (5) respirators with hyperventilation; (6) septicemia, particularly gram-negative sepsis; (7) salicylate intoxication.

A mild degree of respiratory alkalosis is a common finding in a high percentage of postoperative patients and is often associated with some degree of metabolic alkalosis as well.[18]

Severe respiratory alkalosis produces hypocapneic vasoconstriction (which reduces cerebral circulation) and hypoxia by decreasing the release of oxygen from hemoglobin and decreasing capillary P_{CO_2}, with the production of excess lactic acid. In addition, depression of the ionization of calcium may lead to tetany, and the fall in plasma potassium leads to cardiac arrhythmias and may induce digitalis intoxication. With circulatory failure, there is rapid conversion to a severe and often lethal metabolic acidosis.

The compensation for respiratory alkalosis is renal with the excretion of sodium bicarbonate in the urine. However, sodium retention and antidiuresis following trauma substantially or completely block this compensation and, as a result, an alkaline urine is seldom seen.

Treatment of Respiratory Alkalosis. A mild degree of alkalosis, partially respiratory in origin, is seen in a large percentage of postoperative patients upon whom blood-gas analysis is performed. In general, these patients have good cardiac, pulmonary, and renal function and will recover without treatment. The development of respiratory alkalosis may be an early clinical indication of the presence of septicemia and should lead the observant physician to institute vigorous antibiotic therapy if other indications of sepsis are present. Severe respiratory alkalosis has a poor prognosis owing to the underlying causes of the hyperventilation. Within the limits imposed by oxygen demand, narcotics have proved effective in reducing ventilation. Theoretically, the inhalation of an oxygen-carbon dioxide mixture, with sufficient CO_2 to raise the P_{CO_2} to normal, should be effective. In the few instances tried, patients have tolerated this procedure poorly.

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Metabolic Abnormalities of Shock

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Alterations in metabolism produced by decreased blood flow, circulatory failure, or shock may be considered from the standpoint of what happens to the individual as a whole, what happens in each organ system, and changes in the parenchymal cells of each organ. Metabolic changes of the entire organism will be reflected in changes in the constituents of the blood with varying contributions or deficiencies by the several organs. Metabolic changes in individual organs may be reflected in changes in functions of that organ and often can be measured in man. Abnormalities of metabolism of cells and subcellular organelles can presently only be studied in detail in experimental animals with occasional measurements in man where tissue can be sampled. The metabolic abnormalities of shock are secondary changes resulting from decreased blood flow, decreased oxygen and nutrient delivery to tissue, and decreased removal of waste products. These circulatory problems are modified or augmented by complex neuroendocrine activity, by sepsis, by altered nutrition, and by other changes. Thus, metabolic abnormalities are inextricably related to, produced by, or produce the abnormalities described in other articles in this symposium, such as acid-base balance, endocrine responses, energy metabolism, body water, and others. Finally, all changes produced by shock can be considered metabolic abnormalities since they result from changes in cell function and metabolism. The following is a description of metabolic changes with shock, their impact in the individual, and what might be done about them.

SYSTEMIC ABNORMALITIES IN MAN

Loss of blood volume, if it occurs slowly or if only a small amount is lost rapidly, will produce circulatory adjustments to maintain blood flow. The primary mechanisms to maintain or increase effective circulating blood volume after a loss are: (1) vasoconstriction of capacitance vessels, primarily in the splanchnic bed in man; (2) capillary refilling of blood volume from extracellular fluid according to the Starling hypothesis.

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When Skillman et al.[25] and Hanson et al.[13] studied normal men who were bled 15 per cent of their blood volume (average of 800 ml) they found transient decreases in cardiac output and blood pressure but very few metabolic changes. There was no increase in blood lactate and only transient small increases in blood glucose from 87±4 to 103±5 mg per cent. Free fatty acids increased and reached a peak 3 hours after bleeding (from 1351±205 μEq per L control to 1782±192 μEq per L at 3 hours). If such compensatory mechanisms cannot maintain blood volume and flow or if there are other factors which produce shock, circulatory adjustments will occur which maintain blood flow as much as possible in the central circulation of the heart and brain and reduce blood flow to muscle, kidneys, liver, and splanchnic bed. Reduced oxygen delivery will decrease aerobic cellular metabolism through the Krebs cycle and electron transport system in these organs and energy needs will be supplied increasingly by anaerobic glycolysis. Lactate production will then increase and lactate will not be metabolized adequately by the liver, resulting in increased lactate levels in the blood and lactic or metabolic acidosis.[22] Blood pH decreases below 7.4 as hydrogen ion production from lactic acid continues. This stimulates ventilation which may partially compensate for the metabolic acidosis by blowing off carbon dioxide from the lungs and restoring pH back toward normal. This results in a low Pco_2 or partial pressure of CO_2 in arterial blood. Thus, a patient with arterial blood gas measurements of a pH of 7.3 and a Pco_2 of 22 mm Hg would be characterized as having partially compensated metabolic acidosis. In a patient without diabetes, these measurements are pathognomonic of an inadequate circulation. Oxygen consumption by such a patient would be decreased. With hypovolemic shock and cardiogenic shock, oxygen consumption decreases because delivery to the periphery is decreased. Oxygen extraction in the periphery then increases so that the arterial and mixed venous oxygen content difference ($A—Vo_2$) is large. In septic shock initially, at least, when the circulation is hyperdynamic (high cardiac output), the $A—Vo_2$ difference is small, indicating that either the oxygen isn't getting to the tissues or is not being used if it does get there. Blood glucose levels are usually increased initially because of increased epinephrine secretion from the adrenal medulla which produces increased breakdown of glycogen in the liver. This hyperglycemia may persist because the pancreas does not respond appropriately with increased insulin secretion. Patients during and after injury and shock have a diabetic type glucose tolerance curve and some insulin resistance. Later in the course of shock there may be hypoglycemia. If severe shock continues or persists, lactate levels will be extremely high and ventilatory compensation for this acidosis will not be adequate. The pH may reach levels of 7.0–7.1. The measurement of extremely high lactate levels has been used as an indication that the patient will not survive.[28] Weil et al. found that when blood lactate levels in patients were above 4.5 mM, survival was less than 50 per cent, and when the level was above 12.0 mM the mortality was over 95 per cent. However, it is unwise to make an assumption about a patient not surviving from a laboratory measurement even though such measurements do indicate severe cell anoxia. In man, pure hypovolemic shock due to blood volume loss or to extracellular fluid loss, such as with intestinal obstruc-

tion, seldom occurs in pure culture because there usually is tissue injury as well. It is difficult to separate the effects of hypovolemic shock and decreased blood flow alone from various aspects of direct cell and organ injury.

ORGAN FUNCTION ABNORMALITIES IN MAN

During the Korean Conflict, the United States Army Surgical Research Team[16] carried out studies of various organ systems to determine how they functioned immediately after severe injury, particularly when associated with shock. The changes which they described were probably related to decreased blood flow to the particular organ system and, therefore, can be considered metabolic depression of that organ. In the blood there tends to be a fall in serum sodium and a rise in serum potassium, although these do not reach dangerous levels unless therapy is inappropriate or there is renal failure. Eosinophils are low, indicating activation of the adrenal axis. There is depression of liver function as evidenced by an increase in bilirubin in the blood. This is especially true when shock has been present and when blood transfusions have been given. BSP retention is increased. There is an abnormal cephalin flocculation test and later there tends to be an increase in globulin and a decrease in albumin. The Army investigators found that for a few days after injury the gallbladder tended not to visualize by oral cholecystography, suggesting decreased function. There was an increase in muscle metabolism generally with increased urinary creatinine excretion but little increase in creatine unless there was direct muscle injury. This group also found that the oral glucose tolerance curve had a diabetic type shape after injury and the insulin tolerance curve was flattened indicating some resistance to insulin. Pancreatic function was studied also by measuring amylase levels and if there was no direct injury to the pancreas, the amylase levels in the blood tended to be low.

Gastric and salivary secretion tended to be decreased and there was decreased hydrochloric acid production after injury. Alterations in the kidney with shock will be taken up elsewhere. With decreased blood flow to the kidneys urinary output will decrease as will glomerular filtration rate and prerenal azotemia may occur with a rise in blood urea nitrogen. Creatinine levels in the blood should not increase greatly unless there is renal damage which may progress on to acute renal failure.

With shock, decreased coronary blood flow may contribute to a further decrease in cardiac output. The heart under normal circumstances extracts more oxygen from blood passing through it than do other organs. It is, therefore, more vulnerable to decreased blood flow because it cannot greatly increase oxygen extraction as can other tissues and organs. This is particularly a threat in patients with coronary artery disease where the coronary circulation cannot vasodilate in an autoregulatory way in response to decreased cardiac output. If the heart becomes ischemic, it may produce lactate rather than utilize lactate in its metabolism and there may be an alteration in the utilization of free fatty acids which the heart uses for its metabolic needs. If shock persists and is severe, no matter

what the initial cause, there may ultimately be depression of the heart or myocardium. This would be expressed clinically by a low cardiac output and a high or rising venous pressure.

Much has been written about the effects of shock on the lung, leading to terms such as "shock-lung." The lung is fairly resistant to ischemia and it is unlikely that pure hypovolemic or hemorrhagic shock per se produces significant damage to the lung. The lung is exposed to oxygen in the air breathed and whatever cardiac output there is passes directly through the pulmonary circulation. In men studied in the Vietnam War, hemorrhagic shock was not associated with a high incidence of pulmonary dysfunction. However, shock associated with severe tissue injury of the extremities, thorax and abdomen, and particularly septic shock, has been associated with a high incidence of pulmonary dysfunction leading to the term "post-traumatic pulmonary insufficiency." It is better to use this term rather than "shock-lung" because decreased blood flow per se does not seem to be a factor which significantly damages the lung or produces metabolic abnormalities within it. Little is known about alterations in the metabolism of the brain with circulatory failure other than that the sensorium and electroencephalographic activity may be depressed. The effects on vital centers are not well understood.

Deysine et al.[8] have reported significant decreases in serum albumin averaging 1.4 gm during clinical episodes of septicemia or septic shock. Whether this is due to depression of the synthetic function of the liver in producing albumin or loss of albumin into the areas of sepsis is not well understood. Recently Cunningham, Shires, and Wagner[6] have reported that severe hemorrhagic shock of significant duration in man is associated with alterations in the red blood cells with an elevation of the internal sodium concentration. The mean red cell sodium concentration was 7.5±2.1 mEq per L of packed red cells in normal subjects, but in patients with severe hypotension for longer than 1 to 2 hours, this value increased to 17.0± 5.8 mEq per L. The authors speculate that this change may be only one manifestation of a process that involves a generalized change in cell composition and function during hemorrhagic shock.

CELLULAR METABOLIC ABNORMALITIES IN SHOCK

In recent years it has been possible to utilize various basic science techniques and measure the metabolic and biochemical changes in cells from various organs during shock.[2, 23] At the present time almost all of the studies have to be carried out in experimental animals where invasive measurements could be made and tissues could be sampled frequently and in significant quantities. Such studies have been carried out in a number of laboratories and have now provided a more coherent picture of the progression of events in a cell as the blood flow to it decreases.[2, 17] There is initial depression of cell function and then alterations in various aspects of that cell's function leading eventually to death of the cell. Haldane once said that "anoxia not only stops the machine but wrecks the machinery." With decreased blood flow to an organ its function is de-

pressed. If decreased blood flow continues, then changes take place which jeopardize survival of that organ. This progression of events can best be determined by studying cellular function. The information presently available supports the following hypothesis: The initial alteration in a cell, as blood flow around it decreases and oxygen delivery, nutrient delivery, and waste product removal are decreased, is a change in the function of the cell membrane. Shires[24] and his group measured the potential difference across the cell membrane utilizing an ultramicroelectrode which could be inserted inside the cell. With prolonged and severe hemorrhagic shock in the dog, the resting transmembrane potential of a muscle cell decreased from −90 mv to −60 mv. With this change in potential difference one can predict according to the chloride space and Nernst equation that sodium and water enter the cell and potassium comes out. In addition, Shires and his group have sampled with a micropipette the interstitial tissue around muscle from an animal in shock. They find that potassium reaches extremely high levels of 15 to 18 mEq per L after 120 minutes of shock, suggesting again that with severe prolonged shock, potassium is leaving the cell as the membrane potential decreases. This increase in interstitial fluid potassium is not reflected in potassium levels in plasma.

In our laboratory, we measured the transport capability of cells of the liver of the rat by in vitro techniques and found that in prolonged hemorrhagic shock there is decreased capability to transport sodium and potassium.[21] In late shock, the liver cells have lost the capability to exclude sodium and maintain intracellular potassium concentrations. These cells seem, therefore, to lose potassium and take up sodium and probably water along with it. The magnitude of these changes in water movement into cells is probably not large. It would be estimated, for example, that the increase in intracellular water by such a change in membrane potential in man in severe and prolonged shock may be of the order of magnitude of 2 liters, which would only be 10 per cent or less of extracellular fluid volume. As membrane potential and transport capability are altered, the enzyme system Na-K ATP-ase which seems to be responsible for sodium and potassium transport has greatly increased activity, probably in response to increased sodium getting into the cell. As this happens the high energy phosphate compound adenosine triphosphate (ATP) is utilized in increasing amounts. The intracellular organelles called mitochondria which produce most of the ATP or energy within the cell are stimulated to increase ATP production. Further sodium gets into the cell and also into mitochondria and potassium is lost. ATP levels within the cell begin to decrease. The levels of cyclic AMP begin to decrease and may produce alterations in the effects of various hormones such as insulin, glucagon, catecholamines, and perhaps the corticosteroids. As the sequence of cell injury with decreased blood flow continues, the cell tends to swell, the mitochondria swell, and the endoplasmic reticulum swells. Metabolic capability is further decreased, less ATP is produced because of the shift to anaerobic glycolysis and less oxidative metabolism. This leads, therefore, to increased lactic acid production. Mitochondrial function becomes abnormal. Fewer two-carbon fragments (acetyl-CoA) are burned and bro-

ken down to carbon dioxide and water. Further deterioration continues and eventually the intracellular organelles called lysosomes begin to break down and leak. The lysosomes contain hydrolytic enzymes and these may be involved in further damage inside the cell. There is evidence, also, that the lysosomal enzymes can get out of the cell and circulate and may produce damage to neighboring cells or other organs. Eventually the cell is destroyed and, as this happens, other toxic factors may be released which can make this a vicious cycle, altering adjoining cells or other tissues and organs. Associated with these progressive functional and metabolic alterations in the cell, morphologic changes can be seen by electron microscopy in the cell with hemorrhagic shock. Some years ago Holden[14] and his group described the cell swelling, mitochondrial swelling, and endoplasmic reticulum swelling seen in hemorrhagic shock in the rat. In their studies they compared hemorrhagic shock with severe hypoxia in the rat and found very few morphologic changes with hypoxia alone. More recently Trump[2] and his group have studied the progressive changes seen in various cells of patients with shock. These studies were carried out after death by an immediate autopsy technique. They found that virtually all of the acute responses of cells to injury such as shock involved alterations of the membrane systems. Early changes that they described after injury include clumping of nuclear chromatin, dilatation of the endoplasmic reticulum, and swelling of the cell sap. This can be correlated with increased cellular sodium, decreased potassium, and increased water. In this phase, also, the cell membrane is unstable and may form blebs at the surface. First the mitochondria shrink and become more electron-dense and then later they begin to swell. As this swelling continues the process becomes irreversible with clumps of dense material appearing in mitochondria, interruptions in the cell membrane, and lysis. Finally, the cell is converted to a mass of debris with huge inclusions resembling myelin occurring and the cell becomes necrotic. In our laboratory we have found large decreases in ATP levels in muscle, in the liver, and in the kidney, with prolonged hemorrhagic shock. We have also noted decreased protein synthesis in the liver, and resistance of the muscle membrane to the effects of insulin in promoting glucose uptake by the muscle. These progressive and interrelated effects on cell function will occur in any organ where blood flow is decreased and form a cycle of alterations progressing on to cell and organ death. These studies are beginning to lead to more specific approaches to treatment.

MEASUREMENTS REQUIRED IN PATIENT CARE

Since the primary problem producing metabolic defects in hypovolemic shock and other forms of circulatory failure is decreased blood flow, the primary measurements needed to provide adequate care of patients are those which document the adequacy or inadequacy of blood flow. The minimum measurements needed are: continuous monitoring of arterial blood pressure and central venous pressure, monitoring of the electrocardiogram, and repeated measurements of cardiac output by the

indicator dilution technique using either dye or thermal dilution, particularly to document improvement in the circulation during various treatment programs. Although the measurement of cardiac output has in recent years been considered to be a measurement for clinical research, it has now been amply documented that it is extremely useful particularly in difficult problems of shock where the patient does not respond adequately and rapidly to simple resuscitative measures. In addition to these measurements, adequacy of the peripheral circulation should be documented by observation of the patient, his skin, extremities, and peripheral pulses and by measurement of urinary output and urine studies. Continuous measurements of urine output and urine study serve as the best indicators of adequate organ perfusion, particularly because the kidney is sensitive to decreased blood flow. If adequate blood flow to the kidney and therefore adequate renal function are maintained, it is likely that there will be adequate blood flow to the gut, liver, and other organs as well. The overall metabolic status of the patient and adequacy of the circulation in providing for oxygen and metabolic needs can best be determined by serial measurements of the partial pressures of oxygen and carbon dioxide and the pH of arterial blood. Not only will this give valuable information about the adequacy of oxygenation of arterial blood but also about the development of metabolic acidosis as well. Although the measurement of blood lactate levels is interesting, it is not essential for adequate care of patients. The measurement of mixed venous oxygen content in the low right atrium or in the pulmonary artery can be compared with the arterial oxygen content to give some idea about oxygen extraction and utilization in the periphery, but is not a critical measurement for good patient care. In addition to the measurement of central venous pressure by a catheter in the right atrium, it may also be necessary in some patients to insert a catheter such as the Swann-Ganz balloon-tipped catheter into the pulmonary artery by way of the right atrium and right ventricle in order to measure pulmonary artery pressure. By wedging the catheter in a small pulmonary artery with the balloon inflated, the pulmonary artery wedge pressure can be measured, and provides a reasonable reflection of left atrial pressure. There are complex circulatory failure problems where there may be a difference in right and left atrial pressure and treatment may vary accordingly. This is particularly true in individuals with serious liver disease, with pulmonary emboli, with coronary artery disease, and with other types of cardiac failure.

Measurements of other changes in the blood which may reflect the function of particular organs such as the BUN, creatinine, bilirubin, etc., may be helpful in the care of injured patients but do not add very much during the initial care of a patient with severe shock.

TREATMENT

The cornerstone of treatment of the metabolic defects produced by shock is restoration of normal circulation.[1] Thus, the initial assessment, monitoring, and observation of the patient must be directed towards de-

termining the status of the circulation. Measurements should determine whether the patient has hypovolemia as evidenced by a low central venous pressure and/or a low left atrial pressure along with an inadequate arterial circulation, or whether the circulatory problem is primarily that of cardiac failure with an elevated central venous pressure or of sepsis with an elevated temperature and a hyperdynamic circulation with an increased cardiac output which is still inadequate. However, no matter what the cause of shock, the possibility of hypovolemia must be considered first. Patients with circulatory failure should be treated initially by an attempt at increasing vascular volume before any other measures are carried out. If the central venous pressure and/or left atrial pressure is low or even normal, volume replacement should be given initially to try to restore a reasonable arterial circulation and tissue perfusion by increasing the effective circulating blood volume. In this regard, it is necessary to remember that, even though a patient has no evidence of loss of blood volume or loss of extracellular fluid by vomiting or sequestration with intestinal obstruction, the increasing of blood volume may be helpful. Thus, a patient with an acute myocardial infarction may have previously received digitalis and diuretics and have a low central venous pressure and would respond to some volume replacement. The septic patient may have previously been volume depleted and respond to increased vascular volume.

The concept of an effective circulating blood volume should be used. Measurement of the actual blood volume at any particular time is not as helpful as is the response of the circulation to increasing its volume. Obviously, when the central venous pressure and/or left atrial pressure begin to rise and reach high levels, volume replacement must be slowed or stopped.

The type of fluid to be given is determined by what is lost. In the initial resuscitation of an injured patient who has lost blood, Ringer's lactate solution is the best fluid to give. Several liters can be given while blood is being prepared by cross-matching for that patient. If the blood loss has been less than 1000 to 1500 ml, resuscitation with only Ringer's lactate solution may be quite adequate. If blood loss has been greater than this or is continuing, then whole bank blood may be necessary. If exsanguinating hemorrhage continues, immediate blood transfusion with type-specific blood which has not been crossmatched may be necessary as an emergency procedure. In other situations of hypovolemia where there has been vomiting, intestinal obstruction, or other sequestration of fluids, Ringer's lactate solution is the most appropriate replacement solution. The specific treatment of other forms of shock such as cardiogenic shock and septic shock are taken up in other articles. If the initial problem was hypovolemic shock and volume replacement is given to a point where central venous pressure rises to high levels but the arterial circulation and organ perfusion are still inadequate, then other measures will be needed. Inotropic agents such as isoproterenol or epinephrine to increase contractility of the heart and other support measures are the next agents to be used.

As volume replacement is being given, arterial blood gas and pH measurements should be made. If the pH is below 7.3, one or two ampules of sodium bicarbonate may be given intravenously along with continued volume replacement. However, the metabolic acidosis produced by shock will be corrected fairly rapidly by volume replacement if an adequate circulation is restored. If an adequate circulation is not restored by volume replacement or other drugs as needed, the buffering agent, sodium bicarbonate, will provide only a transient response. Sodium bicarbonate will certainly elevate the pH back towards normal but the pH will soon decrease again unless the circulation is restored. Thus, correction of metabolic acidosis must be considered to be an adjunctive measure rather than a primary approach to the treatment of hypovolemic shock. If large numbers of blood transfusions are necessary in resuscitating a hypovolemic patient and the circulation is then restored and maintained in that individual, the citrate in the bank blood will be metabolized to bicarbonate. Such a patient will then develop metabolic alkalosis with a pH above 7.4. It must be emphasized that the arterial blood pH is an indicator of adequacy of the peripheral circulation but correction of it alone may not necessarily improve the circulation. Metabolic acidosis has been thought to be harmful and to further depress the circulation. Evidence for this was gained from studies of severe respiratory acidosis particularly where acid infusions have been given to experimental animals. These have been found to decrease myocardial contractile force and cardiac output, to decrease cardiovascular responsiveness to catecholamines, particularly vasoconstrictors, to produce vasodilation and hyperkalemia, and to increase the susceptibility to ventricular fibrillation. Others, however, have found no change in myocardial contractility and responsiveness to catecholamines and also found that cardiac output was either increased or showed little change until extremely low pH levels were reached. These discrepancies in experimental information are caused in part by differences in response when an isolated organ or intact animal is studied. In the intact individual with metabolic acidosis, catecholamine secretion is increased, and may compensate for some of these depressant effects. Feins and Del Guercio[9] found that cardiac output and myocardial function increased in patients in whom mild metabolic acidosis developed during operation with an arterial pH of 7.28. The most important problem caused by severe acidosis in man may be the propensity to cardiac arrest or ventricular fibrillation. In a study of clinical shock, Smith[26] and his associates found no direct relationship between acidosis and the inability of the individual to maintain a reasonable blood pressure. Thus severe acidosis should be corrected along with volume replacement. However, sodium bicarbonate should not be given empirically without measurement of arterial blood pH. In years past, the organic buffer, THAM, or tris-hydroxymethoaminomethane, was used for a brief period because it was thought to correct intracellular acidosis as well. Although intracellular acidosis is still not well documented or its effects known, THAM at the present time is not recommended because it has no particular advantage. In addition, it may depress ventilation, decrease

arterial oxygen saturation and produce hyperkalemia. In addition to volume replacement and correction of severe acidosis, supplemental oxygen should be given to such patients to provide the benefit of a small increase in dissolved oxygen and arterial Po_2. In pure hypovolemic shock the patient may be ventilating satisfactorily and adequately oxygenating his arterial blood. The problem then is delivery of oxygen to the tissues, rather than oxygenation of arterial blood. However, supplemental oxygen by nasal catheter or mask may provide some small advantage. Vasoactive drugs and, specifically, vasoconstrictor drugs should be avoided, particularly until volume replacement has been adequate, as evidenced by a high or increasing central venous pressure. Then if the circulation has not improved, a vasoactive agent may be needed. It is best to use a drug which increases cardiac contractility such as one of the rapidly acting digitalis preparations and isoproterenol or epinephrine by a slow intravenous drip.

The volume of fluids used to replace a loss may exceed that estimated or measured to be lost. Although rough estimates of volume replacement needs may be made, it is best to replace losses by determining what is needed to maintain an adequate circulation rather than by using some predetermined formula.

A particularly exciting area of clinical and animal research for resuscitation and care of patients now and in the future is that of correction of the various metabolic problems and alterations in cell function described previously. If a depressed circulation, such as with hypovolemic shock, alters cell function by decreasing cell membrane capability and decreasing energy capability within the cell, then this can be considered a form of energy crisis for the cells and various organ systems.[3] Thus, attempts are being made to provide for these needs by:

1. Providing substrates or compounds which provide for energy production within the cell under adverse circumstances. This would include the use of hypertonic glucose, producing increased glycogen stores, and other approaches.
2. Providing energy directly by the utilization of the high energy phosphate compound ATP.
3. Utilizing solutions which provide protection or help for the cell membrane and its functions. These include the so-called polarizing solutions containing glucose, potassium, insulin, and steroids.
4. Using metabolic retardants such as potassium which may provide protection against ischemia by depolarizing the cell membrane.

Evidence for a beneficial effect of hypertonic glucose solutions in hemorrhagic shock has been provided by Moffat et al.[18] where they found survival in dogs was significantly prolonged with such treatment. Fritz and Fitts[10] demonstrated increased survival after hemorrhagic shock in sheep treated with hypertonic glucose. Six of 11 animals survived in a control group who received their shed blood and Ringer's lactate solution, but 12 of 12 animals survived who received, in addition, hypertonic glucose solution. However, Gump et al.[12] found that when radioactive-tagged hypertonic glucose was given to the dog in hemorrhagic shock, it was not metabolized. This raises the question as to whether the hypertonic glucose solution actually served as a substrate for energy metabolism or simply provided a hemodynamic effect by its osmotic characteristics.

Protection for the myocardium against anoxia by increasing the myocardial glycogen content of dogs with a fat diet was demonstrated by Hewitt et al.[14] They found that cardiac function after 5 minutes of anoxia was significantly better in animals with increased glycogen stores. Allopurinol, a xanthine-oxidase inhibitor which could preserve purine bases for ATP production, was found to have a beneficial effect for experimental myocardial ischemia by DeWall et al.[7] The intravenous injection of allopurinol after ligation of the left anterior descending coronary artery in the dog resulted in improvement in appearance of the myocardium, a more normal EKG, increased myocardial contractility, and fewer arrhythmias. Pindyck et al.[20] gave glucose, 1 gm per kg body weight, intravenously over a 30-minute period to seriously ill patients and found an improvement in myocardial function in patients who had previously received only 5 per cent dextrose in water. There was no improvement in these patients if mannitol was given or if the patients had previously received 2000 calories per day in the form of 50 per cent glucose intravenously. Much more work remains to be done to determine exactly how these substrates are producing their beneficial effects. It is suspected that much of their positive or beneficial effect is due to circulatory improvement rather than by providing energy substrate.

In studies from our laboratory, we have demonstrated that giving the high energy phosphate compound ATP complexed with magnesium chloride to rats in hemorrhagic shock improved survival, rapidly increased the energy levels within cells of the liver, kidney, and muscle back to normal levels, and corrected the insulin resistance produced by shock.[4, 5]

When a small amount of ATP-$MgCl_2$ was given to rats after a prolonged period of shock, 75 per cent of the animals survived. If the animals were given only their shed blood, or their shed blood plus Ringer's lactate solution or the breakdown product of ATP, such as ADP or AMP, none survived. When ATP-$MgCl_2$ was given to animals after a period of shock, the ATP levels increased from 0.24 to 1.79 μ moles per gm of tissue in the liver and from 0.24 to 1.04 μ moles in the kidney. Although this is an interesting observation that energy might be provided to cells which are anoxic and have reduced energy levels, caution must be observed in interpretation of these data. ATP with magnesium chloride may have a profound circulatory effect and this may be its primary effect rather than providing energy per se.

A number of studies have been carried out using polarizing solutions containing glucose, insulin, and potassium with or without steroids in various patient populations. Moffitt et al.[19] compared a group of patients having cardiac operations who received such solutions with patients who did not. There were very few differences between the patient groups. The primary differences were that total ketone bodies were reduced in the patients receiving this solution and plasma potassium levels were significantly increased.

Weisul et al.[29] infused glucose, potassium, and insulin solutions into six patients with low cardiac outputs and septic shock and found that there was improvement in myocardial performance with this treatment

which was not provided by the use of isoproterenol. After administration of glucose/potassium/insulin, several changes were apparent. Mean arterial pressure was significantly increased although the value was less than expected. Mean pulmonary artery pressure showed little change and both pulmonary wedge pressure (10.1±3.4 mmHg) and central venous pressure (7.5±2.0 mmHg) were significantly reduced. Cardiac index (5.23±1.55) was increased to 350 per cent of the septic shock value. Stroke volume index (47.1±12.9 ml per beat per m^2) was increased to values greater than expected in normal man. While isoproterenol therapy modestly increased myocardial work at lower filling pressures, both right and left ventricular stroke work increased after the administration of glucose/potassium/insulin. None of the patients died in the septic shock state after the administration of glucose/potassium/insulin, but deaths did occur more than 3 days later as a result of other causes. Thus there is considerable excitement about the possibility of this approach in the treatment of low-flow states when fluid replacement and drug therapy have not been effective.

Potassium has been utilized to protect the myocardium particularly during organ perfusion or during periods when it is necessary to arrest the heart during cardiac operations.[11] Potassium seems to depolarize the membrane and to provide some protective effect.

These approaches and the hypotheses on which they are based are fascinating to contemplate but most difficult to prove. The mainstays of treatment of shock will continue to be restoration and maintenance of an adequate blood volume, blood flow, and oxygen transport and delivery. More specific methods for support of cell function and energy metabolism may well be forthcoming.

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Metabolic Adaptations for Energy Production During Trauma and Sepsis

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Recovery from trauma with extensive bacterial infection requires a vigorous response by metabolically active cells and tissues. High cardiac output, maintenance of blood volume and hematocrit, increased metabolic rate with or without fever, synthesis of immune proteins, and the proliferation and antibacterial activity of immunocompetent cells, maintenance of adequate pulmonary ventilation, in addition to cellular and wound repair, all require provision of metabolic energy sources and necessary biosynthetic precursors. The biochemical adaptation evoked by the body to provide these necessary materials is unique to the post-traumatic or septic state, and differs in important respects from the physiologic responses to fasting, starvation, exercise, cold, or other conditions.

This review focuses on the major metabolic consequences of trauma and sepsis, examines the control mechanisms which are disrupted, and suggests possible biochemical explanations for certain components of the response. It is so arranged that first the general features of the response are described, and the consequences of them are discussed; subsequently the detailed mechanisms are presented with laboratory and clinical data and with relevant biochemical explanations.

THE METABOLIC RESPONSE: OVERALL CHARACTERISTICS

The Injury

Major trauma, such as a crushing injury with fractured bones, severe burns, prolonged hemorrhagic shock, or severe infection, elicits a general metabolic response with essentially the same pattern in all

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cases, although certain minor aspects differ according to the type of injury. Endotoxin (a lipopolysaccharide extracted from cell walls of gram-negative bacteria) also elicits metabolic abnormalities, but the pattern is somewhat different from that observed with trauma and sepsis. Species differences have also been noted in certain components of the response to different types of injury. This review focuses upon those responses which appear to be common to the various forms of injury, and which are most likely to pertain to humans. However, some extrapolation of data will be necessary because much of the experimental work has been done with animals using a diversity of models, and adequate human correlation is not uniformly available.

Type of Response

Preconvalescent or preanabolic stages of the response to injury have been variously divided according to the adequacy (or timing) of the observed defensive mechanisms. During sepsis in man, two types of response can be easily identified: a low flow response (characterized by low cardiac output, low body temperature and metabolic rate, as well as the endocrine and biochemical changes shown in Table 1), and a high flow response (characterized by high cardiac output, elevated metabolic rate, usually accompanied by fever, plus the endocrine and biochemical changes in Table 1). The low flow state is common early after a traumatic injury or later as a failure to adequately resolve infection or tissue damage. It is similar in many respects to the "ebb" and "necrobiotic" phases described by Cuthbertson,[20] while the high flow response is similar to Cuthbertson's "flow" phase. Moore[71] subdivided the flow phase into a "catabolic" phase, lasting for 3 to 7 days after an initial "injury" phase, followed by a "turning point" phase of a few days, and terminating in an anabolic phase. This review is primarily concerned with the catabolic, high flow phase of injury, and other phases will be specifically identified when they are under discussion.

The General Metabolic Response

Glucose Metabolism. The metabolic effects of trauma and sepsis are predominantly catabolic. Glucose and amino acid metabolism are disrupted at both the systemic and cellular levels. Diabetic type glucose

Table 1. *Responses in Man During Sepsis*

INJURY, EBB, LOW FLOW, OR NECROBIOTIC PHASE	CHRONIC, FLOW, HIGHFLOW PHASE
↓ Metabolic rate	↑ Metabolic rate
↓ Body temperature	↑ Body temperature
↓ Blood insulin	↑ Blood insulin (compared to fasting)
↑ Blood catecholamine levels	Normal or slightly ↑ blood catecholamines
↑ Blood glucose (except in terminal stage)	Normal or slightly ↑ blood glucose
↑ Blood lactate	Normal or slightly ↑ blood lactate
↑ Blood fatty acids	↓ Blood fatty acids (compared to low flow and fasting states)

tolerance has been commonly observed[40, 46] despite normal[59] or accentuated[51, 80, 87] insulin secretion in response to the administered sugar. Injected insulin failed to produce the expected decline in blood sugar after severe trauma,[46, 77] although after minor to moderate trauma a delayed fall of normal magnitude was observed.[39] Glucose, normally potent in suppressing nitrogen loss when administered to fasting individuals, was relatively ineffective during the catabolic phase of trauma and sepsis.[7, 8] However, this resistance was overcome by administration of large amounts of glucose, together with high doses of insulin, which reversed the nitrogen catabolism in severely burned patients.[43] The slowed glucose disappearance rate, the relative ineffectiveness of injected insulin, and the need for high doses of insulin to reduce the nitrogen loss after injury probably are indications of resistance by the tissues to the action of insulin. Resistance to the effects of insulin on tissue glucose utilization has been observed in tissues isolated from septic fasted rabbits, septic fasted rats,[83] and posthemorrhagic shock rabbits[84] (Fig. 1). Muscle appeared to have undergone a greater relative loss of sensitivity to insulin than did adipose tissue in correlation with the previous findings;[83] an observation which may be significant, as explained in a subsequent section of this review.

Paradoxically, basal glucose oxidation and turnover rates are increased,[61] and fasting blood glucose levels are normal or only slightly elevated,[59, 61] while basal circulating insulin levels may be as much as three-fold higher than normal[17, 75, 83] during the peak of the insulin-resistant, glucose-intolerant, nitrogen catabolic response to major injury or sepsis. It should be noted that a relatively normal blood glucose level maintained by a 2 to 3-fold elevation of insulin suggests that tissue uptake of glucose requires greater insulin stimulation to achieve the normal blood glucose levels, and not an inability of the pancreatic beta cells to secrete adequate amounts of insulin.

The situation observed after glucose administration to post-trauma subjects, a normal or accentuated insulin secretory response[51, 59, 80, 87] concomitant with slowed glucose disappearance, probably also signifies a failure of tissue glucose uptake rather than a pancreatic insufficiency.

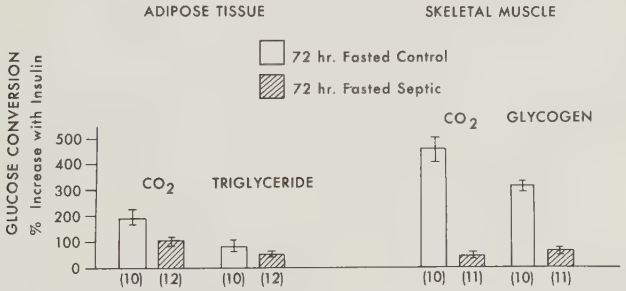

Figure 1. The effect of insulin on the utilization of glucose by isolated adipose and muscle tissues from control-fasted and septic-fasted rabbits. Data is reported as Mean ± S.E.M. with the number of observations in parentheses. The effect of insulin was significantly less in the septic groups in each study, by Student's t-test, $p < 0.01$, except adipose tissue triglyceride which was significant, $p < 0.05$.

Although the resulting increase in ratio of blood glucose to insulin can be construed conversely[69, 70, 88] as a "relative" hypoinsulinemia (relative to the prevailing blood glucose), the failure of normally sufficient levels of insulin to promote a normal rate of glucose assimilation indicates the basic inability of insulin to stimulate tissue glucose utilization.

The failure of insulin to reach the supranormal concentrations necessary for normal rates of glucose uptake can only be regarded as a secondary insufficiency unmasked by the increased insulin requirement, perhaps similar to the unmasking of a diabetic-like state during obesity which disappears when the increased insulin requirement is abrogated by weight reduction.[78, 79]

The low flow (ebb, shock, or injury) phase differs from the high flow period described above in that it is characterized by hyperglycemia and hypoinsulinemia.[16, 73] These effects are probably the result of adrenergic stimulation of hepatic glycogenolysis and simultaneous suppression of insulin secretion.[57] Accordingly, premedication with a ganglionic blocking agent[37] or surgical denervation of the adrenal medulla[38] prevented the hyperglycemia of shock, and restored insulin secretory activity.[42] Failure to observe elevated plasma alpha-amino nitrogen levels, and marked depletion of glycogen stores suggest that these early changes in blood glucose probably result from glycogen mobilization and do not require postulation of increased gluconeogenesis from amino acids.[89, 90]

Many of the changes observed during the low flow phase may be the result of tissue anoxia.[86] Consequently, the low flow response is characterized by reduced oxidation of glucose,[41, 91] fatty acids,[92] and pyruvate[92] and elevated levels of lactate.[18, 64, 92]

Stoner and co-workers,[92] studying rats in shock following hind limb ischemia, found evidence of reduced Krebs cycle activity after bilateral hind limb ischemia, but found relatively normal glycolytic activity. Pyruvate produced by glycolysis seldom accumulates in the cell and, if not combusted to CO_2 by the reactions of the Krebs cycle, is usually converted to lactate and released to the circulation. This process may contribute to the increased blood lactate characteristic of the low flow response to sepsis.[18, 64]

Protein and Amino Acid Metabolism. Imbalances of protein and amino acid metabolism during prolonged sepsis probably have greater impact on the welfare of the individual than do the concurrent disturbances of glucose and lipid metabolism. Body protein components undergo rapid hydrolysis and the resulting amino acids are broken down to the carbon skeletons plus the nitrogen component, most of which appears in the urine as urea. Urinary nitrogen excretion becomes massive, attaining levels as high as 25 gm of nitrogen a day.[72] Howard and associates, studying humans suffering long bone fractures, demonstrated that total nitrogen losses averaged 190 gm of nitrogen per 70 kg man, equivalent to a loss of almost 6 kg of lean body mass.[44, 45] Sepsis is a stimulus par excellence for the mobilization of body nitrogenous components, and the very highest rates are observed in the septic, posttraumatic subject.[53]

The carbon chains derived from the mobilized amino acids are used, for the most part, for energy production by the tissues, either directly or after prior conversion to glucose or lipid substances. The energy available from the amount of utilized amino acids (indicated by the degree of negative nitrogen balance) roughly corresponds to the heat produced as a result of the increased metabolic rate after trauma.[12] Reduction of metabolic expenditure or maintenance of burned or injured subjects at elevated ambient temperatures results in a reduction in the rate of nitrogen loss.[13] These facts and the close correspondence in the timing between the increased metabolic rate and the nitrogen loss,[23, 94] plus the fact that the increase in both nitrogen excretion and metabolic rate is eliminated in protein depleted rats, have led to an association of these two events. It is certainly possible that the rapid mobilization of body protein is necessitated, at least in part, by increased energy demands during the hypermetabolic period which usually precedes recovery from major injury or infection.

Duke and co-workers have calculated that an increased proportion of the expended calories are derived from protein sources after injury.[24] This is supported by the observation of a mean respiratory quotient for injured individuals in the range of 0.83 to 0.85, suggesting that the end products of protein catabolism are a major source of energy for the tissues after trauma.

Considerable amounts of data have established the source of most of the mobilized protein to be body musculature. The very magnitude of the response suggested the source to be muscle. The nitrogen/sulfur and nitrogen/potassium ratios,[22] plus the concomitant creatinuria[32] supported this conclusion. Recent studies have shown directly that the muscle tissue is depleted of protein, while visceral protein is spared. The protein content of liver and kidney of rats with infections was maintained despite profound general catabolism and weight loss,[81] and burned rats showed increased liver protein content and turnover rate while carcass protein was markedly depleted.[58] This occurs in correlation with evidence of increased hepatic protein synthesis,[60, 95] while conversely, muscle microsomal protein synthesis was reduced after femur fracture in rats.[102] The different effects of trauma and sepsis on peripheral and visceral protein metabolism result in what has been termed a peripheral to visceral translocation of protein,[3, 54] and represent the exact opposite of the response to fasting. In the fasted rat, visceral protein is extensively depleted before muscle protein begins to be utilized.[14, 31] Septic fasted rats showed the relative preservation of liver mass and protein content compared to fasted controls in accordance with this concept (Table 2).

Consequences of a Prolonged Catabolic Response

Following minor injury or uncomplicated elective surgery, the catabolic phase is usually brief and of no serious consequence to a normal, well nourished patient. However, if this catabolic state occurs in individuals previously weakened by age, malnutrition, or disease or if the

Table 2. *Liver Mass and Protein Content in Septic Fasted and Fasted Control Rats*

	FED	72 HOUR FASTED	72 HOUR FASTED WITH PERITONITIS
Total liver weight per 100 grams final body weight	4.2 ± 0.4 (13)	3.1 ± 0.2 (13)	4.4 ± 0.5 (12)
		0.001	0.001
		NS	
Protein as percent of liver weight	21.0 ± 2.1 (13)	23.9 ± 2.2 (13)	20.9 ± 13 (12)
		0.01	0.01
		NS	
Phosphoenol pyruvate carboxykinase μmoles/min/g. prot.	11.8 ± 4.4 (10)	24.7 ± 4.6 (10)	28.8 ± 3.1 (16)
		0.001	0.02
		0.001	

period of rapid catabolism is prolonged by a complicated injury, by infection, or by subsequent injury, then the large loss of body protein becomes a threat to the individual's survival. Even in previously healthy, well nourished patients, acute loss of 30 per cent of the body weight is associated with almost total mortality.[93] Prolonged protein catabolism results in muscle weakness (contributing to inadequate pulmonary ventilation and cardiovascular insufficiency), reduced immune system potency, and eventually to loss of wound strength and improper healing.

The purpose of filling the energy demands of the individual by a rapid post-trauma mobilization of peripheral protein has not been clearly established. Greater requirements for glucose probably exist, but fulfilling the glucose requirements therapeutically, even to the point of inducing hyperglycemia, results in only a minor improvement in the negative nitrogen balance.[10] This is in direct contrast to the potent effect of glucose in reversing the negative nitrogen balance when administered to fasting normal subjects.[34] The availability of amino acids for protein biosynthesis is another likely purpose of the protein hydrolysis, and it is of interest in this regard that administration of amino acids ameliorates the nitrogen catabolic state.[1, 2]

A personal opinion is that injury of moderate severity requires some protein hydrolysis to provide optimal levels of glucose and amino acids, but this useful and appropriate response becomes exaggerated after very severe injury, to the point of becoming harmful. The pressures of genetic evolution could not anticipate the metabolic needs of patients

receiving modern medical care, and it is those individuals most dependent on medical intervention which show the most debilitating side effects of the protein catabolic state. According to this interpretation, the catabolic response is physiologically necessary and appropriate in the starved, moderately injured subject, but may become unnecessary and harmful for the hospitalized, severely injured patient receiving exogenous (usually intravenous) nutrition.

THE BIOCHEMICAL BASIS OF THE METABOLIC RESPONSE

The observed abnormalities of blood metabolite concentrations and the sustained breakdown of lean body mass with the consequent increase in urinary nitrogen excretion, all reflect basic alterations in the utilization of fuels and synthetic precursors at the tissue and cellular levels. This section will explore these changes with reference to the biochemical mechanisms underlying the observed abnormalities.

Glucose Utilization

Glucose and its metabolites are vital to the overall economy of body energy generation. Glucose is ordinarily the primary, and in some cases the sole, energy source for several important tissues, including the red and white blood cells, the renal medulla, bone marrow, the reticuloendothelial system, and nerve tissue—especially the human brain which consumes 90 per cent of the metabolized glucose during early fasting.[7] When blood flow to the area of a wound is interrupted or reduced, glucose becomes a critical substrate for support of the healing process. Many other tissues are able to depend on fatty acids to supply a major portion of their energy source, but nevertheless require some glucose metabolism to provide essential intermediates for intracellular biochemical processes.

Most of the glucose metabolized undergoes one of two principal routes of degradation: terminal combustion, with the carbon atoms appearing as CO_2; or reversible fragmentation to pyruvate, usually appearing in the form of the pyruvate metabolites, alanine and lactate (Fig. 2).

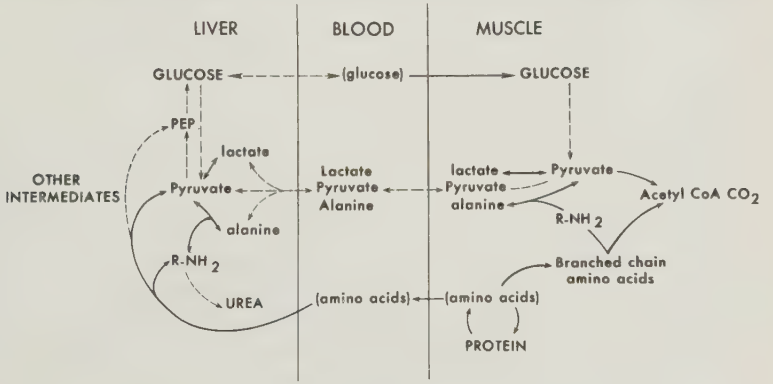

Figure 2. Several important metabolic pathways influenced by sepsis and trauma.

Pyruvate, alanine, and lactate are all particularly good substrates for hepatic gluconeogenesis, and are therefore rapidly transformed and reappear as blood glucose. Thus, unlike terminal combustion to form CO_2, cleavage of glucose to pyruvate and its derivatives does not result in irreversible loss of glucose from the body's fuel economy, and this route is favorable in situations requiring conservation of available glucose supplies.

Effect of Trauma and Sepsis. All indications are that metabolism becomes more heavily dependent on glucose utilization during recovery from major trauma or sepsis. Glucose oxidation and turnover rates are increased concomitant with elevated blood sugar levels.[61] The large urea excretion indicates the production of glucose from amino acids, and increased lactate levels and turnover rate[6] suggest increased nonoxidative glycolysis. Accumulation of lactate in the blood of injured individuals has been negatively correlated with survival,[18, 64] and indicates a failure of hepatic uptake to keep pace with metabolite production, probably because of a marked increase in the rate of peripheral lactate release. Marked increases in blood lactate are probably associated with the entry of the individual into the "low flow" state.[19]

Gluconeogenesis

The rate of glucose production by the liver is primarily determined by the available supply of precursor substances under normal circumstances. Elevated blood levels of lactate, pyruvate, or alanine are all associated with a corresponding increase in hepatic glucose synthesis. Alanine in particular appears to have a singular influence in the control of glucose synthetic rate. It alone constituted almost 50 per cent of the total amino acids extracted by the liver[29] during fasting. The physiologic role of alanine is further demonstrated by the observations that the rate of glucose production by perfused liver was greatest when alanine was the amino acid substrate,[65, 82] the rate of glucose output varied with relation to substrate concentration within the physiologic range more in the case of alanine than in the case of most other amino acids,[65] and alanine administration to humans resulted in the prompt appearance of label in blood glucose.[25, 56] Furthermore, glucagon stimulated the hepatic uptake of alanine more than that of any other amino acid.[66] Conversely, increased glucose and insulin levels powerfully reduced hepatic alanine extraction, an effect mediated by a reduced fractional alanine extraction since arterial alanine levels did not decrease.[29]

Hormonal Control of Gluconeogenesis. Hormonal stimulation of hepatic glucose production is primarily exerted by glucagon and epinephrine, by virtue of their ability to promote hepatocellular cyclic-AMP accumulation.[26, 27] On a molar basis, glucagon is ten times more potent than epinephrine in this action.[27] Adrenal steroids affect gluconeogenesis in two ways; they exert a permissive action for the rapid, short-term changes induced by cAMP, and they provide a stimulus for slowly developing, but longer lasting enzymatic adaptations facilitating increased hepatic gluconeogenesis.[9] Steroids may also increase peripheral release of precursor substances by direct action on muscle tissue

protein synthesis.[35] However, steroids appear to be unable to account for the post-trauma increase in protein catabolism, because adrenalectomy with replacement therapy (for the permissive effect) failed to abolish the nitrogen excretion associated with fracture.[15]

The facilitation of gluconeogenesis by glucagon and epinephrine appears to result from an increased conversion of three carbon precursors to phosphoenol pyruvate.[26] The enzyme immediately responsible for the synthesis of this compound, phosphoenol pyruvate carboxykinase, was increased to a greater degree in 72-hour, septic fasted rats than in control 72-hour fasted animals, especially when the higher liver weight of the septic animals is considered (see Table 2).

Insulin and elevated blood glucose levels oppose the action of epinephrine and glucagon on hepatic gluconeogenesis by several mechanisms. High levels of glucose favor production of glycogen and may directly inhibit gluconeogenic enzymes. Insulin, in the presence of glucose, decreases hepatocellular cAMP,[26] opposes the activation of gluconeogenic regulatory enzymes,[66] and may suppress precursor extraction from the blood, particularly that of alanine.[28]

The counter-regulatory influences of insulin and glucagon have led to a concept of the control hepatic gluconeogenesis by the prevailing insulin-glucagon (I:G) ratio.[96] When blood glucose is high, amino acid stimulation of insulin secretion is potentiated, while glucagon secretion is suppressed, resulting in a high insulin-glucagon ratio which in turn suppresses glucose synthesis and diverts amino acids to protein synthetic processes. Conversely, when blood glucose is low, incoming amino acids stimulate, at most, a moderate increase in insulin, but a large glucagon secretion, resulting in a low I:G ratio promoting conversion of the amino acids to glucose. This economical mechanism favors glucose synthesis when blood sugar levels are low, but conserves amino acids for protein formation when adequate levels of glucose are present.

After major trauma, sepsis, or other injuries, the insulin:glucagon ratio is low, therefore favoring amino acid conversion to glucose. However, the hepatic effects of these hormones cannot alone explain accelerated gluconeogenesis after trauma. Increased extraction of precursors would be expected to reduce blood substrate concentrations, unless a corresponding increase in peripheral amino acid release occurred. As discussed earlier, a lower substrate concentration decreases the rate of gluconeogenesis. Consequently, a new steady state will be established at a lower blood substrate level, but with a net turnover still determined by the rate of peripheral precursor input (or else the level would continue to fall) (Fig. 3). Accordingly, glucagon infusion resulted in a brief increase in urinary nitrogen excretion as blood amino acid levels fell, followed by a restoration of the preinfusion rate of catabolism as a new steady state was established.[30]

Effect of Trauma and Sepsis on Hepatic Gluconeogenesis. Glucose production by the liver was maintained at normal or elevated rates during the high flow response to trauma or sepsis,[36, 48, 61] in association with increased rates of precursor turnover.[61] Studies with animal models of sepsis have also shown increased total hepatic blood flow,

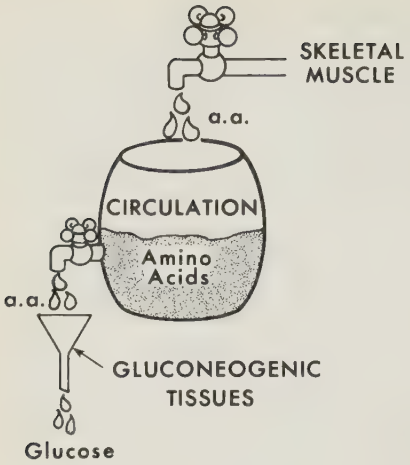

Figure 3. Determination of gluconeogenic rate by substrate concentration at constant precursor concentration. According to the diagram, a change in either valve would alter the level of amino acids (a.a.). Opening the lower valve (gluconeogenesis) would decrease the level in the barrel, while opening only the top valve would result in an increased level. Since the rate of outflow changes as the level (pressure) changes a new steady state is established, with the net rate of flux determined by the rate of inflow when the level (a.a. concentration) is constant. Both valves could open or close with no change in level, but with marked change in flux. However, at any constant level, it is the rate of influx which determines the rate of outflow in the control of gluconeogenesis.

increased hepatic oxygen consumption, accelerated uptake of alanine and lactate, and continued glucose output during the high flow state.[47]

It is interesting to note that the low flow state is characterized by the converse findings; all of the parameters listed for the animal experiments above were either not increased or were below the normal (nonseptic) fasting values, while gluconeogenic precursors accumulated in the blood.[47, 48] It is also interesting that the administration of endotoxin produced a response which is highly similar to the low flow response.[97]

Hepatic gluconeogenesis during the high flow response is probably augmented as a result of increased peripheral substrate release in conjunction with a low insulin-glucagon ratio which facilitates an accelerated hepatic precursor uptake and conversion to glucose. The gluconeogenic response and the consequent urinary nitrogen loss with trauma and sepsis therefore depend in a large measure on the mechanisms of peripheral amino acid release.

Peripheral Amino Acid Release

The rate of delivery of amino acids to the liver and consequently the rate of gluconeogenesis depends primarily upon the rate of release of these glucose precursors from the peripheral tissues, especially from skeletal muscle, and this in turn depends upon the dynamic balance of protein synthesis and degradation resulting in either a net uptake or release of amino acids. Muscle tissue of adult humans normally synthesizes and hydrolyses protein at equal rates, on the average, resulting in no net change in muscle protein content or tissue size over extended time periods. A change in the rate of either aspect of this process, alters the dynamic balance and results in either net formation or net degradation of protein. Increased net breakdown can result from decreased synthesis of new protein, increased hydrolysis of preformed protein, or a combination of these processes. Protein turnover is the rate at which breakdown and resynthesis occur and does not depend on the net balance (formation or breakdown) of the process which could be zero (no net change) while turnover rate was high. Evidence will be presented

below indicating accelerated protein turnover and increased net catabolism during intraabdominal sepsis in rabbits.

CONTROL OF PROTEIN TURNOVER IN MUSCLE. Of the large number of factors able to modify protein turnover, precursor availability is the most basic. Unless a full complement of amino acid charged t-RNAs are present, peptide synthesis will proceed only to the point requiring insertion of the absent amino acid. If the appropriate residue is not forthcoming, the synthesis is aborted and the peptide fragment is rapidly degraded. The amino acids which are present, but unable to form a complete protein as the result of the deficiency of one or more of the full amino acid complement, are ultimately either directly utilized as fuel by the tissues or are converted to glucose by the gluconeogenic tissues. The essential amino acid, leucine, one of the three branched chain amino acids (b.c.a.a.), appears to have a special role in this regard in that protein synthetic rate appears to be modulated by minor fluctuations of leucine concentration within the physiologic range.[4, 5]

Metabolic fuel supply also is an important factor in the control of net protein balance. Starvation and strenuous exercise both provoke a net breakdown of protein and consequent release of amino acids into the circulation. In the heart, the depression of protein synthesis associated with diabetes was reversed by provision of ketone bodies or fatty acids.[49] Although these metabolic fuels were unable to overcome the effects of diabetes on skeletal muscle protein synthesis, certainly in less extreme circumstances where insulin is not completely absent, their availability is likely to be necessary for net protein anabolism. An inadequate fuel supply has been proposed to explain net protein breakdown of trauma and sepsis,[1, 2, 83] as discussed below.

HORMONAL CONTROL OF PROTEIN TURNOVER IN MUSCLE. Numerous endocrine hormones influence skeletal and cardiac muscle protein synthesis. Of these, insulin appears to represent the primary control factor in most situations.[10] Insulin has long been recognized to stimulate amino acid uptake by peripheral tissues, to promote amino acid incorporation into protein,[67, 68, 101] and has recently been shown to inhibit intracellular protein hydrolysis.[33] As a result of these activities, insulin inhibits amino acid release from peripheral tissues, and causes a reduction in total circulating amino acid levels. The amino acids removed from the blood disappear in a pattern identical to the amino acid composition of skeletal muscle protein.[62] However, additional factors must influence protein turnover, because a reduction in peripheral amino acid release occurs during prolonged starvation despite very low insulin concentration.

Corticosteroids cause increased amino acid release,[55] decreased uptake and incorporation of amino acid into protein,[99, 100] and increased oxidation of leucine[85] by skeletal muscle, as well as exerting a favorable influence on hepatic conversion of amino acids to glucose. However, it is generally believed that the steroids have primarily a permissive role, and are not responsible for the overall protein catabolism during fasting[9] or with trauma[50, 74] and sepsis.*

*Clowes, G. H. A., Jr.: Personal communication.

Glucagon has no demonstrable effect on protein metabolism by skeletal muscle, despite numerous attempts to show such an action.[6] When infused into normal humans, glucagon had no lasting effect on net nitrogen excretion,[30] indicating no significant action of this hormone in control of peripheral protein mobilization.

Effect of Trauma and Sepsis. The mobilization of protein derived amino acids and catabolism of these with a resulting increase in urinary nitrogen excretion with trauma and sepsis have been discussed, as has the evidence that the bulk of the mobilized protein is derived from skeletal muscle. These data suggest a major translocation of protein from the periphery to the gluconeogenic (and ureogenic) liver and kidney.

Reduced in vivo leucine incorporation into protein in peripheral muscle, concomitant with increased leucine incorporation in liver, has been reported by Lust[63] to occur during bacterial infection in rats. Similarly, Reiss[81] concluded that amino acids derived from accelerated protein breakdown in peripheral muscle provide substrate for increased hepatic protein synthesis and maintenance of liver and kidney protein content in starved rats suffering from pneumonia compared to starved controls. Young and Huang[102] studied protein synthesis by microsomes of muscle derived from a leg contralateral to a fractured femur. When the rats had received adequate prefracture protein nutrition, incorporation of labelled leucine into protein by the microsomal preparation was appreciably reduced, the maximal reduction occurring 48 to 72 hours after fracture, in correlation with the time of maximal nitrogen excretion after fracture in rats.[21] A recent study[76] of body protein metabolism after abdominal surgery using tracer studies of infused leucine indicated relatively normal rates of protein degradation, but suppression of protein synthesis.

Contrary results have recently been obtained by the author studying septic fasted rabbits. As shown in Figure 4, within 72 hours sepsis caused an increase in both protein synthesis and protein degradation (hydrolysis) with the effect on hydrolysis being larger. The data in Figure 4 are based on measured intracellular amino acid specific radioactivity, which changes dramatically in the muscle during sepsis as a result of dilution of the label by an increase in the intracellular amino acid pool size, probably due to the more rapid protein hydrolysis. If presented on the basis of incorporation of label the date in Figure 4 would show a slightly lowered rate of amino acid incorporation, similar to that observed for leucine incorporation, and therefore agree with the previously reported studies[21, 63, 76, 81, 95,] which did not take altered intracellular amino acid specific radioactivity into account (Fig. 5). The concept of specific radioactivity is explained in Figure 6.

Although previous studies failed to detect the increased synthetic rate because of the large change in intracellular amino acid pool size, the conclusions based on the rate of label incorporation probably remain valid. Since degradation of cellular protein was accelerated to a greater degree than was the synthesis of new protein, NET protein synthesis was lower in the septic group and the overall change is effectively what was concluded on the basis of reduced incorporation of label: a loss of tissue protein.

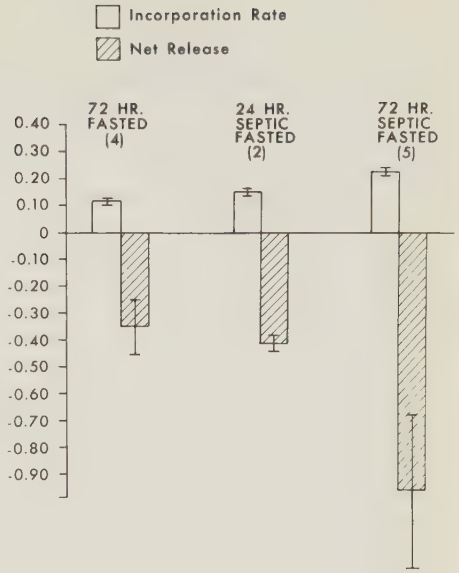

Figure 4. Protein synthesis (incorporation) and net degradation (tyrosine released into medium plus that reincorporated into protein), reported as Mean ± S.D. The 72 hour septic-fasted valves were statistically different from both other groups by Student's t-test, p · 0.01. Data are expressed in nanomoles per hour per milligram tissue.

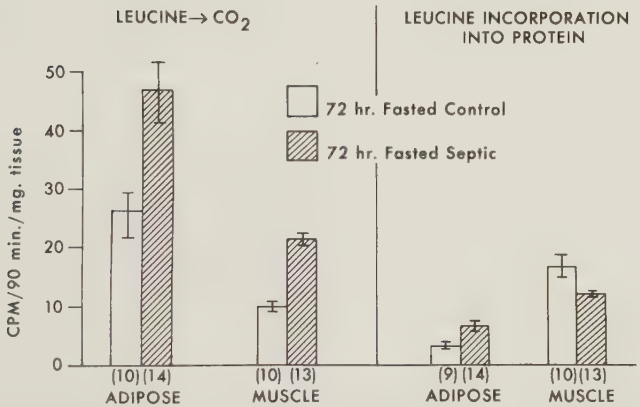

Figure 5. Leucine metabolism by isolated skeletal muscle and adipose tissue from control and septic rabbits. Data are in terms of counts converted to product and are not corrected for specific radioactivity. Mean ± S.D. with number of observation in parentheses. All differences between control and septic groups are significant, $p < 0.01$, by Student's t-test.

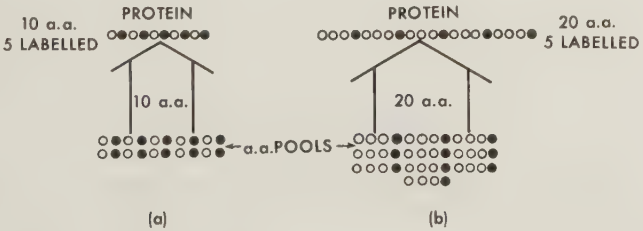

Figure 6. Specific activity changes alter the rate of incorporation of label relative to the rate of total synthesis. In both (a) and (b) five labelled amino acids appear in the finished protein, despite the twice greater rate of synthesis in (b), because only one in four amino acids are radioactive (black dots) in (b) while one in two are labelled in (a).

The Biochemical Basis for the Effect of Trauma and Sepsis: Net Protein Catabolism in Muscle

Trauma and sepsis probably interfere with a number of the control mechanisms responsible for the maintenance of cellular protein levels. The three prime influencing factors – hormones, amino acid supply, and adequate fuels necessary to sustain cellular metabolic processes – probably all contribute to the net protein catabolism observed in the post-trauma or septic state.

Insulin Resistance. The protein anabolic effect of insulin is necessary for muscle to maintain adequate levels of cellular protein, and reduced insulin stimulation results in the mobilization of muscle protein and the release of the resulting amino acids into the blood. Insulin resistance in muscle may have effectively the same influence as reduced insulin levels, a reduction of anabolic signal, because of the inability of the tissue to respond to the circulating insulin. Resistance to the action of insulin on glucose utilization[84] and protein synthesis supports the possibility of such a failure of the tissue to respond to, or to detect, the presence of normal or elevated insulin concentrations.

Irreversible Combustion of Branched Chain Amino Acids. An inadequate supply of any one of the full complement of amino acids necessary for the synthesis of a protein molecule will result in the termination of the synthetic process and the hydrolysis of the nascent peptide fragment. The irreversible combustion of the essential amino acid leucine by fat and muscle tissue is markedly accelerated by sepsis in 72-hour fasted rabbits, a response also noted following hemorrhagic shock[84, 85] (see Fig. 5). The loss of this amino acid, which cannot be synthesized by the body and must come from external sources, would necessarily limit the potential amount of new protein synthesis in individuals receiving no exogenous amino acids. Other amino acids, not able to be utilized as fuel by muscle and not formed into protein because of an insufficient leucine supply, would be expected to be released from muscle to be converted to glucose and urea by the liver. This mechanism could therefore contribute to the increased urea excretion observed following major trauma or sepsis. Leucine removal would be especially significant in view of the particular sensitivity of muscle protein synthesis to the prevailing leucine concentration.[6] However, it should be noted that this mechanism has not been proven, and the increased leucine oxidation may result from (and not cause) the enhanced protein hydrolysis.

Metabolic Fuel Supply. A possible contributing factor which is closely associated with the first two mechanisms is the supply of metabolic fuel to muscle tissue. Muscle is insulin resistant and unable to increase its utilization of glucose in response to insulin stimulation, while simultaneously blood free fatty acids and ketones are below those of normal fasting individuals.[1, 19, 83] The key fuels for muscle are therefore available to it in limited supply during sepsis, and it is possible that the observed increase in the oxidation of leucine (and probably the other branched chain amino acids) may be necessary to supply the energy needs of the tissue.

The inadequate supply of metabolic fuel, postulated above, may result from a differential effect of sepsis on the insulin sensitivity of fat and muscle tissues[83] (see Fig. 1). Muscle showed a more complete suppression of insulin action than did adipose tissue, and since the insulin level is above normal in the septic high flow state, adipose tissue lipolysis may be suppressed (see Table 1). Relative maintenance of adipose tissue deposits during sepsis supports this concept.[83] Thus, the elevated insulin concentration, while unable to adequately stimulate glucose utilization by muscle, may suppress adipose tissue lipolysis, thereby depriving muscle of its normal fuel in the fasting state, lipids. The resultant energy deficit may force the utilization of amino acids for energy production.

CONCLUDING REMARK. The biochemical mechanisms presented in this review are still in the preliminary investigative stage, and many details remain to be resolved before firm establishment of the metabolic physiology of the post-trauma state will be possible. Further studies in this important subject are currently in progress in numerous laboratories. The ultimate resolution of the biochemical mechanisms underlying the metabolic response to injury, and identification of the hormonal or other signals responsible for the observed changes will provide a scientific basis from which to seek the hoped for goal of improved management of the victim of trauma and sepsis.

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The Core Pathobiology and Integrated Medical Science of Adult Acute Respiratory Insufficiency

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A lucid understanding of the core biologic information on which rests the clinically important essentials of acute respiratory insufficiency seen in surgical practice is now attainable on a nonempirical, factual basis. Insights necessary for the rational assessment of (1) clinical symptomatology, (2) early diagnosis, (3) pathophysiology, (4) physiologic monitoring data, (5) therapy of proven value, and (6) prognosis can now be derived to a great extent from knowledge concerning the specific nature, sequence, and progression of human pathologic events. This latter process of piecing together the presumed consecutive or sequential pathologic stages in the course of human disease is specifically known as morphogenesis. Light microscopic morphogenesis has traditionally been the classical foundation and the continuing mainstay for characterizing the (1) natural and (2) therapeutically altered biologic course of human disease processes.[54] This still remains so, despite the introduction of ultra-sophisticated computerized physiologic-biochemical instrumentation; certainly in the subspecialty of pulmonary diseases, modern technology, with all its elaborate automated monitoring capability, has failed to fulfill the informational usefulness and practical predicative potential of its sister field of cardiovascular technology.[76] Thus, pulmonary pathologic-microscopic evaluation remains as the basic science which is most fundamentally useful in the characterization of altered pulmonary function.

Ultrastructure has come to provide a genuinely useful high-magnification extension of knowledge on pathologic events, and ultrastructural morphogenesis has already proven its scientific capability of defining

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sequential pathologic fine cellular alterations from the study of even single biopsy specimens.[30, 54, 69]

This article will start by crystallizing out a simple straightforward sequence of the core facts that the practicing physician should know, and which can be derived as carefully as possible from scientific observations that are clearly germane to human acute respiratory insufficiency.[69] Information generated from controversial and/or artifactual experimental animal models[53] will be cautiously avoided. The article will then continue as an in-depth review of the evidence for the summarily stated morphogenetic and pathophysiologic basis for acute respiratory insufficiency. Despite its blatant imperfections, it will, at the very minimum, represent the first undertaking on the part of a pulmonary pathologist at attempting a comprehensive in-depth review and multidisciplinary-integrated analysis of the subject, utilizing a clinical, pathologic, cell biologic, and physiologic correlative approach.[53] Many of the usual bibliographic references found in recent clinical reviews[5, 16, 36, 46, 51, 55, 75] will be omitted unless they are specifically relevant and noncontroversially contributory to our understanding of the biology and natural course of acute respiratory insufficiency.

THE PATHOLOGIC BASIS FOR THE PATHOPHYSIOLOGY, MANAGEMENT, AND PROGNOSIS OF PROGRESSIVE ACUTE RESPIRATORY INSUFFICIENCY

Core Goals

In summary, the goals of this paper are to demonstrate and allow an understanding of (1) the pathologic basis for the pathophysiology, clinical management, and prognosis of progressive acute respiratory insufficiency (ARI); (2) to indicate that, regardless of inherent vagaries, complexities, and controversies concerning pathogenesis,[51, 38] the fundamental pathologic progression of the many variants of human ARI is essentially the same; (3) to indicate that the sequential pathologic alterations in the progression of ARI can be reasonably well pieced together by studying various light microscopic and ultrastructural morphogenetic stages that may be found in the end-stage pathology, as well as reviewing the early pretreatment pathology as it was documented decades ago;[35, 67, 69] (4) to provide insights, derived from an understanding of morphogenesis, as to why some patients respond to currently standard management while others are refractory; and (5) to define the specific evidence that supports the core conclusions that now follow.

Core Conclusions Concerning the Biologic Course of Acute Respiratory Insufficiency

1. The pathophysiologic common denominator of the many clinical variants of ARI is the nonspecific and limited pulmonary interstitium's reaction to injury; that the interstitial (interalveolar septal) reaction to injury in the common surgical variants of ARI is very similar to the many interstitial medical entities that are categorized as acute interstitial pneumonitis;

2. In ARI seen in relation to sepsis, following "complicated" surgery, burns, resuscitated hemorrhagic shock, nonthoracic trauma, intraabdominal disease with peritonitis or pancreatitis, poisoning, neurogenic injury, aspiration or inhalation injury, oxygen toxicity, etc., all have in common interstitial pulmonary capillary dysfunction, and the degree of increased pulmonary capillary permeability and/or injury, to a great extent, dictates the sequential pathologic alterations;

3. Thus, the pathology, pathophysiology, and certain aspects of management are in many ways closely akin to those of the better known clinical and pathologic spectrum of pulmonary edema;

4. Contrary to widespread belief, true anatomic atelectasis is not greatly contributory to the observed pathophysiology and response to treatment;

5. Specifically, the severity, duration, and potential reversibility of increased pulmonary capillary endothelial permeability and the resultant magnitude and persistence of transcapillary leakage of both fluid and particularly serum protein are the major determinants for the wide variation in clinical course, physiologic (monitoring) parameters, response to treatment, and final outcome;

6. The initial and most reversible clinico-pathologic stage is interstitial pulmonary edema which leads to tachypnea and hyperventilation due presumably to stimulation of reflex interstitial pressure-stretch receptor sites.[42] Respiratory alkalosis results. Loss of normal interalveolar septal elasticity leads to resultant decrease in compliance and premature airway closure due to peribronchiolar edema. Minimal hypoxemia is present. Radiologic findings are minimal as seen in interstitial edema of cardiogenic origin;[27]

7. The intermediate stage is a very high protein-laden intraalveolar edema which is considerably more refractory to treatment than uncomplicated cardiogenic pulmonary edema.[55] The high protein concentration deactivates surfactant-induced foaming[63] and its more viscous plasma-like properties tend to decrease the typical moist rales of cardiogenic pulmonary edema produced in terminal bronchioles. The radiographic picture is that of acinar-filling (white lung in its most severe diffuse form). There is nonventilation of fluid-filled alveoli with markedly decreased ventilation-perfusion ratios and so-called "physiologic shunting" leading to profound hypoxemia.[36] The secondary decrease in alveolar volume which may result in decreased functional residual capacity[47] is an intrinsic secondary feature of intraalveolar edema.[63] The gross picture of the lungs in this stage are heavy, wet, and bulging,[33, 70] not small and atelectatic as suggested in some recent clinical review articles;[47]

8. The more irreversible third stage is the result of the lungs' reactive cellular response to protracted and unrelenting interstitial injury with continuing increased capillary permeability, leading to progressively severe intraalveolar edema protein deposition which becomes inspissated, insolubilized, and compressed against alveolar and respiratory duct walls (hyaline membrane formation). Protracted interstitial injury elicits cuboidal lining cell (granular pneumocytic) hyperplasia[3, 8, 14, 18, 24, 25] and, ultimately, fibrogenesis with deposition of collagen.[22] These restrictive and destructive cellular tissue alterations[41, 52] lead to markedly altered biophysical (bioengineering) three-dimensional structural and functional airway pathodynamics that make maintenance of viable pulmonary function increasingly nonnegotiable, regardless of therapy;

9. The variants of ARI treated by surgeons prior to 1960 and the advent of blood gas monitoring and aggressive respirator support, died with outright massive pulmonary edema.[35, 67] Thus, this end-stage pathologic picture which is indistinguishable from severe, well advanced interstitial pneumonitis with hyaline membranes[33, 36, 54, 69, 70] is not a new disease process discovered during the Vietnam War[51, 61] and given clinical appellations of adult respiratory distress syndrome,[1, 44] post-traumatic pulmonary insufficiency,[36] shock lung,[51] and congestive atelectasis,[23, 60] but a result of iatrogenic modification of the pathology of noncardiogenic pulmonary edema;

10. As will be shown later in detail, the advent of modern pulmonary intensive care, with aggressive mechanical ventilator support, is indeed the factor

responsible for the altered pathology and clinical course (i.e., the biology of the disease) of the surgical variants of ARI. This has been due to two factors: (a) altering distal airway and alveolar pathology, cell biology, and acinar pathophysiology; and (b) the prolongation of the time-course or life, during which these superimposed pathogenetic factors are operative.

Core Pathologic Features of Progressive Acute Respiratory Insufficiency

The gross autopsy picture is characteristic (Fig. 1). The lungs are the heaviest seen in the practice of pathology. They fill the entire thoracic cage, showing no tendency to normal elastic collapse. Their inflational state is essentially that of the functional residual capacity since the lung-filled open chest is in the natural state of normal end-expiration. The weight is generally over 2000 gm, i.e., three to four times normal weight. The external lung surface is bulging, plum-colored, noncrepitant, and of beefy-firm consistency. The cut surface is full and has a semiconsolidated appearance which exudes varying quantities of edema fluid which is directly proportional to the earliness of the pathologic stage. The wet/dry lung weight ratio is always markedly increased. Focal subpleural and parenchymal intraalveolar hemorrhage are usually present. Bronchopneumonia of varying degrees is often present. Gross atelectasis is not discernible in the great majority of cases, unless inflammation-induced obstructive bronchial mucus plugs or compressive pleural effusions are superimposed complications.

The light microscopic picture consists of either massive pulmonary edema in untreated (fatal, early) cases or a histopathologic picture

Figure 1. End-stage acute respiratory insufficiency (ARI). Gross weight 2200 gm (3 to 4 times normal). These are the largest lungs seen in pathology practice. Their bulging semiconsolidated wet parenchyma fills the confines of the thoracic cavity. Focal subpleural hemorrhage is present (*H*).

indistinguishable from fulminant interstitial pneumonitis with prominent hyaline membranes in more end-stage treated cases (Fig. 2).

The interalveolar septae are congested, tortuous, and edematous. They contain scattered lymphocytes and, in occasional septic cases, intracapillary neutrophils may be present, particularly if leukocytosis is present just prior to death. Hyaline membranes are pressed against the walls of alveoli. They are often particularly prominent at the tips of interalveolar septae projecting into alveolar ducts and respiratory bronchioles.[41] Varying degrees of intraalveolar edema fluid stains densely eosinophilic, thus indicating its high protein concentration. Focal intraalveolar hemorrhage is present. Alveolar cuboidal lining cells (granular pneumocytic hyperplasia) become prominent after the fourth or fifth day after interstitial injury. The alveoli may then contain numerous desquamated granular pneumocytes and/or macrophages. There is a focal decrease in the diameter of alveoli which has sometimes been inaccurately referred to as microatelectasis. These latter findings are no more pronounced than those seen in routine cases of severe cardiogenic pulmonary edema.[63] After the fifth or sixth day there is evidence of fibroblastic interstitial proliferation and, thereafter, both interstitial and focal intraalveolar fibrosis may become evident. Within 2 to 3 weeks, one may see the end-stage picture of chronic interstitial pneumonitis, resembling idiopathic pulmonary fibrosis or the so-called Hamman-Rich syndrome.[29, 52, 62] In rare, extreme instances, focal but total alveolar destruction and disorganization, called "honeycombing," which is indistinguishable from very advanced and end-stage chronic interstitial lung disease, may be found. In the late stages, the gross picture may then thus be that of a more contracted lung as a result of significant fibrosis.[53]

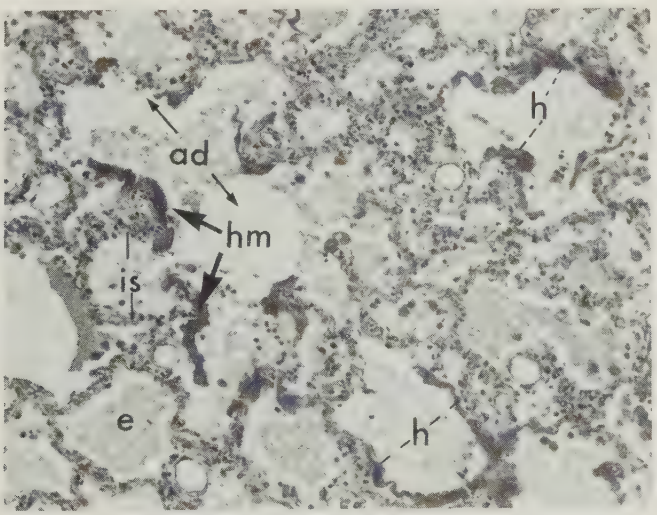

Figure 2. Typical microscopic appearance of treated fatal ARI on day 4. There is pulmonary congestion, intraalveolar protein-laden edema (*e*), hyaline membrane formation (*h*), particularly prominent at the tips (*hm*) of interalveolar septa (*is*) projecting into the alveolar duct (*ad*). The diameters of volumes of the edematous alveoli vary considerably. (120×)

Focal terminal bronchopneumonia is almost always invariably present. However, severe widespread bronchopneumonia of clinically significant proportions may often contribute to the end-stage clinical-pathologic picture.

Diagnostic Interpretation at Autopsy

The picture of vigorously treated progressive ARI is that of a severe interstitial pneumonitis with morphologic indications of markedly increased capillary permeability. Fulminant fatal viral influenzal pneumonitis or acute interstitial pneumonitis as esoteric as inhalation of hot mercury fumes may show an indistinguishable light microscopical picture.[62] Thus, the findings are very distinctive but they are not diagnostic out of context of a correlative clinical setting (i.e., resuscitated shock, trauma, sepsis, and other usual antecedent causes of ARI). If the latter clinical features are absent, the pathologist must pay more attention to taking viral cultures and consider other possible serologic or clinical-pathologic clues that might indicate various other medical etiologic causes of fulminant interstitial pneumonitis.

Gross Atelectasis in Surgical Practice

Basal gross atelectasis is commonly seen in surgical practice when ARI is not present. Bronchiolar mucus stagnation, leading to obstruction and gas reabsorption, may occur. Basal alveolar collapse may occur due to early airway closure (increased closing volume) in postsurgical patients with decreased functional residual capacity due to such things as abdominal distension, or simply due to their lying in the supine position. Older patients with intrinsically high closing volumes are particularly vulnerable. Absorptive atelectasis occurs more readily in patients administered increased concentrations of oxygen. Compressive atelectasis may result from serious pleural effusions due to resuscitative fluid overload and/or incipient heart failure. Regardless of etiology, basal atelectasis readily responds to conservative, nonaggressive management. Atelectasis has no relationship to progressive ARI (so-called posttraumatic pulmonary insufficiency or adult respiratory distress syndrome) that is the main process under discussion in this article.

So-Called Congestive Atelectasis—A Distinct But Very Uncommon True "Pathologic" Entity

The term congestive atelectasis has been used interchangeably, but erroneously, in relation to the usual pathology seen in progressive ARI. Jenkins, Moyer, et al. coined the entity with a distinctive anatomic ring on the basis of somewhat nondescript pathology;[23] the term has unfortunately gained literary momentum, due to its overzealous use by numerous authors investigating experimental hemorrhagic shock in dogs.[51] Congestive atelectasis is the species-specific pulmonary pathologic reaction in the ubiquitously used dog shock experimental model.[60] Unwarranted extrapolations of fact from dog to man based on this artifactual system has generated considerable misinformation in the literature. Despite the misuses and abuses of the term, which has virtually obscured its mean-

ingfulness, there is indeed a very definite, specific, but relatively rare human pathologic entity of *true congestive atelectasis*. The hallmark autopsy feature of large irregular, nonsegmental foci of gross atelectasis diffusely scattered throughout as much as 50 per cent of the otherwise relatively normal lung parenchyma is unmistakably distinctive (Fig. 3*A*). Microscopically, airless, completely collapsed alveoli, characteristic of true anatomic atelectasis, is present (Fig. 3*B*). Gross areas of the retracted, airless parenchyma account for the smallness of the lung, in contradistinction to the huge lungs of the common form of progressive ARI (compare Figs. 3*A* and 1). Martin et al., and Teplitz, have described true congestive atelectasis as a rare (3 per cent) cause of post-traumatic pulmonary insufficiency in Vietnam battle casualties[33] and burn patients,[67] respectively.

Congestive atelectasis, however, is a particularly important potentially lethal pathologic entity in burned children. The association of constrictive circumferential chest burns and congestive atelectasis in children has been previously described by the author.[67] In a series of 38 fatally burned children autopsied at the U.S. Army Surgical Research Unit, in the prepulmonary intensive care era (1961–1963), eight of 13 (62 per cent) dying with constrictive circumferential chest burns had severe conges-

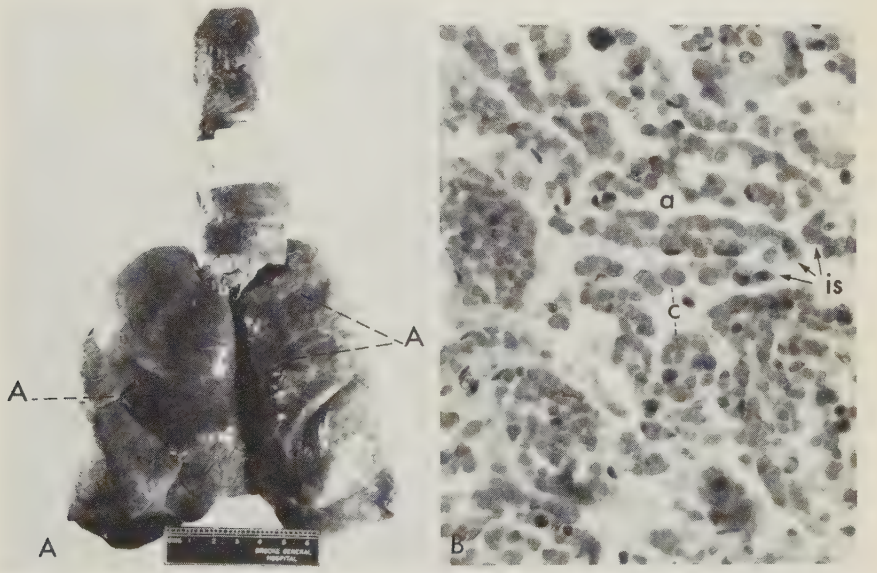

Figure 3. *A*, Classic congestive atelectasis seen in an 11-year-old girl dying with severe hypoxemia and constrictive circumferential chest burn eschar, 11 days post-thermal injury. Patchy, airless, retracted, and shrunken pulmonary parenchyma (*A*) are distributed diffusely and nonsegmentally, involving over 50 per cent of the parenchyma.

B, Classic histologic atelectasis (seen in lungs of Fig. 3*A*) with interalveolar septa (*is*) containing congested capillaries (*c*) which are virtually apposed to one another, with only slit-like intervening alveoli (*a*). Total collapse and airlessness of alveoli (*a*) characterize *true* anatomic atelectasis. (480×)

tive atelectasis leading to progressive fatal pulmonary insufficiency. No such cases were found among the 25 autopsied children without circumferential chest burns. Recognition of this distinct clinical-pathologic entity in burned children is one that warrants careful attention, since modern ventilatory support, with or without thoracic escharotomy, should be life-saving. The role of the constrictive-restrictive effects of the chest wall eschar in preventing normal volume expansion of the chest cannot be avoided, as at least a contributory explanation for its pathogenesis. Circumferential chest burns in adults were not associated with the disorder. The pathogenesis of this morphologic curiosity in adults is unknown, but its rarity and its inability to be diagnosed during life should virtually eliminate the unjustified usage of the term in the adult surgical literature.

TRACHEOBRONCHIAL COMPLICATIONS LEADING TO ATELECTASIS. Major atelectasis may occur as a result of endotracheal tube insertion into the right mainstem bronchus.[13] It is not a rare complication of low-lying tracheostomy cannula insertion in children.[73] Compressive massive atelectasis, secondary to pneumothorax, can be a complication of tracheobronchial intubation of any type as well as mechanical ventilation. In burns, infected tracheostomy sites may lead to necrotizing tracheobronchitis with atelectasis.[72] In severe tracheobronchitis due to the inhalation of certain specific noxious fumes, obstruction due to mucus secretion and sloughed mucosa may result.[33]

Tracheobronchial and Alveolar Injury Due to Inhalation of Noxious Fumes and "Burns"

Direct thermal burn injury can affect the upper respiratory tract only down to the larynx.[67] The inhalation of exceedingly hot steam, with its significantly greater heat-carrying capacity as compared to air, may rarely be the cause of lower tracheobronchial injury, with possible affliction of terminal distal airways.[37] The inhalation of carbon monoxide from certain specific forms of combustion is a cause of rapid lethal hypoxemia that leaves no pulmonary pathologic stigma. Inhalation injury usually occurs in a closed space, although outdoor petroleum explosions may also lead to tracheobronchitis.[50] Certain specific noxious fumes, such as those that arise from mattress fires and other very specific products of combustion, may lead to devastating, diffuse, chemical, tracheobronchial bronchiolitis which is often refractory to any form of treatment. Finally, specific fumes such as high concentrations of nitrogen and sulphur dioxide may lead to severe interstitial alveolar damage with pulmonary edema.[28] As was amply demonstrated by survivors of the famous Coconut Grove disaster, covering of the mouth and nose with a wet cloth is the only measure known to prevent lung inhalation injury.[15] Finally, many forms of nonspecific smoke inhalation which do not contain definitive noxious products of combustion usually cause only mild bronchospasm and mucus secretion, which is rapidly and spontaneously reversible.

Pathologic Observations Regarding the Presumed Presence of Anatomic Atelectasis As a Cause of "Physiologic Shunting" in the Common Type of Progressive Acute Respiratory Insufficiency

Gross basilar atelectasis is no more common in fatal cases of progressive ARI that is found as an incidental finding in random general hospital autopsy populations. The role of atelectasis in ARI was originally emphasized by authors with special research interest in surfactant or dog "shock lung."

More lately, numerous authors have accepted its existence as fact to explain the rationale for the use of PEEP in ARI.[47] Orell described the absence of atelectasis in a series of 20 cases of fatal adult respiratory distress syndrome.[41] Bachoften and Weibel also failed to find atelectasis.[3] Martin et al. described minimal gross basal atelectasis in less than 15 per cent of patients dying with resuscitated hemorrhagic shock and trauma in Vietnam casualties.[33] Teplitz' findings were identical in a large series of fatal burns.[67] There was no association with recognizable or clinical pulmonary symptomatology or insufficiency in either series. In review of the entire pathology literature relating to shock, trauma, and post-traumatic pulmonary insufficiency, seen as early as World War I, one can find no solidly acceptable documentation of diffuse or appreciable gross atelectasis as a significant pathologic finding. Moon, in his classic autopsy study of World War II military personnel dying with all variants of shock and injury predisposing to ARI, clearly documented that the constant and predominant finding was severe pulmonary edema and congestion.[35] In his large series where treatment was often not administered, patients died in the earlier stages of their disease and, therefore, the reported autopsy findings have considerable current scientific importance with regard to what may or may not be seen in the early untreated stages of ARI. Moon alluded to the presence of atelectasis in a small minority of patients although he emphasized its frequency following the specific entity of heat stroke where it is now well known to be a common finding. When one carefully reviews Moon's report,[35] it is clear from looking at the single published illustration* that what was labelled "slight atelectasis," was, in retrospect, scattered microscopic clusters of alveoli which had abnormally small volumes of the type secondary to edema rather than true atelectasis as seen in Figure 3*B*. Some authors have imprecisely used the term focal incomplete collapse or microatelectasis for this observation. The reported illustration of so-called partial alveolar collapse† is in fact identical to that depicted in Figure 6*A*, which is from the lung of a patient who died from rapidly fatal cardiogenic pulmonary edema. The finding of focally decreased alveolar volume is evident in virtually all cases of congestive heart failure with cardiogenic pulmonary edema which occur in younger patients without emphysema, where there is intact normal in-

*Fig. 15, p. 269.[35]
†p. 268.

teralveolar elasticity.[63, 71] It has also been noted by the author in massive noncardiogenic edema seen in vigorously resuscitated large burns.[67] In pulmonary edema, transudation of fluid and protein into alveoli is known to affect alveolar size, presumably due in part to surface tension alterations and other complex biophysical reasons. Staub has correctly stated the issue as follows:[63]

> It should be emphasized that the alveoli in pulmonary edema are not atelectatic, but are fluid-filled at a volume less than their normal volume at a given inflation pressure. They do not contain air and therefore act as unventilated regions of the lung. This explains some of the reports of so-called alveolar closure in pulmonary edema that responds to positive pressure breathing. . . . The high positive pressure does not drive fluid back into blood from alveolar gas space. It accomplishes its effects by inflating the alveolus, spreading the intraalveolar fluid in a thin film over the alveolar wall, permitting the alveolus to be ventilated and oxygen to diffuse into adjacent pulmonary capillaries. As soon as the positive pressure is removed, the alveolus may return to its original condition.

This precise description of the pathologic observations as we too have observed them would, of course, explain the known reduction in FRC which occurs in both ARI and pulmonary edema,[43, 80] and its rapid reversal with CPPB or PEEP.[4, 34] To reaffirm the facts as they exist both in pulmonary edema and the lungs seen in progressive ARI, reduction in volume of alveoli in no way constitutes true anatomic atelectasis or "alveolar (airless) collapse" as atelectasis is strictly pathologically defined. Much confusion and misunderstanding concerning the pathophysiology of ARI can be averted by clarification of this point, which is no small semantic squabble. It is misleading to refer to pulmonary edema with purely secondary focally decreased alveolar volume as being the equivalent of pathologic anatomic atelectasis.

It has been well known for decades that noncardiogenic pulmonary edema (where one cannot treat the easy-to-alter increased left atrial pressure) is more resistant to management than cardiogenic pulmonary edema and may, therefore, need CPPB, as opposed to digitalis and diuretics for reversal.[4, 59] Finally, in treated cases of ARI where large ventilatory volumes, high pressures, and high concentrations of oxygen are used up to the time of death, one might expect a rather extreme degree of generalized atelectasis to be present at death since there is no pressure to now keep the alveoli from collapsing and the prior superimposed absorption of the nearly pure oxygen in the alveolar gas should have led to widespread absorption atelectasis. The documented absence of atelectasis as reviewed above is a monumental paradox for those who remain so firmly entrenched in the unfounded conviction that atelectasis must be present, as an important component of progressive ARI.

Pulmonary Congestion and Edema (Increased Capillary Permeability)

The prominent findings in the lungs of ventilator-treated ARI are congestion, interstitial and intraalveolar edema, focal intraalveolar hemorrhage, and diffuse hyaline membrane formation composed of inspissated plasma protein. These constant characteristics of "wet lung" are clear pathogenetic indicators of increased pulmonary capillary permeability. An attempt to explain the ultra-structural morphogenesis of

increased capillary permeability and pulmonary edema in the setting of ARI was first attempted by the author at the National Academy of Science Symposium on Pulmonary Effects of Non-Thoracic Trauma in 1968.[68, 70]

Gas exchange occurs across the thin interalveolar septal air-blood interface or barrier, which is composed of an attenuated capillary endothelial layer, narrow basement membrane, and outer flat epithelial alveolar lining. These continuous layers split widely to form the broad interstitial compartment which contains collagen, elastic fibers, and fibrocytes, interspersed within mucopolysaccharide ground substance (Fig. 4, *A* and *B*). Capillary endothelial cells are joined together by mucopolysaccharide-filled gaps measuring approximately 40 Å in width, across which the normally constant transvascular filtration of water solute and small protein molecules diffuses into the interstitial compart-

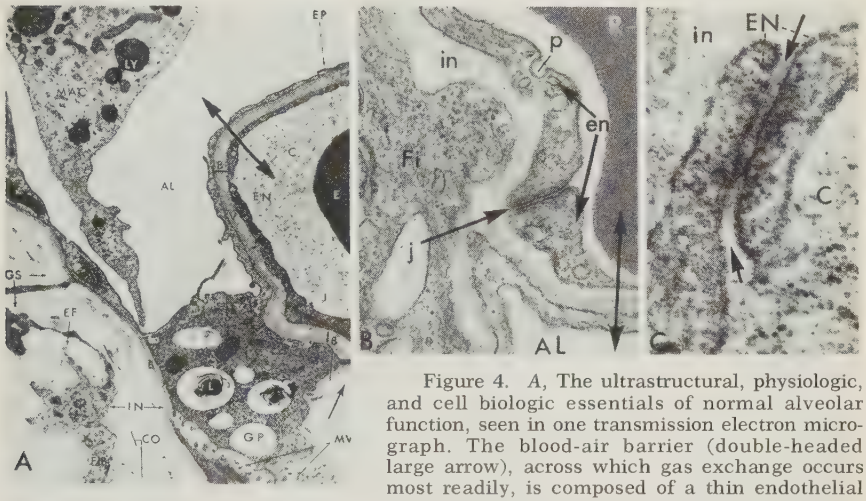

Figure 4. *A*, The ultrastructural, physiologic, and cell biologic essentials of normal alveolar function, seen in one transmission electron micrograph. The blood-air barrier (double-headed large arrow), across which gas exchange occurs most readily, is composed of a thin endothelial layer (*EN*), basement membrane (*B*), and an outer elongate thin alveolar epithelial lining cell (*EP*). A curved dark interendothelial junction (*J*) is present at the right lower aspect of the capillary. The alveolus (*AL*) contains a pulmonary macrophage (*MAC*) filled with lysosomes (*LY*). At the bottom right, a granular pneumocyte (*GP*) secretes surfactant phospholipid present in black lamellar bodies (*L*). The widened interstitial compartment (*In*) contains ground substance (*GS*), collagen (*CO*), elastic fibers (*EF*), and a fibroblast (*FIB*). The junction of the blood-air barrier and the broader portion of the interstitium are seen at the lower right portion of the micrograph (small arrow). (19,000×)

B, Normal ultrastructural cellular components of alveolus (*AL*) and interalveolar septum. Blood-air barrier at right bottom is indicated by the double-headed arrow indicating pathway of gas diffusion. Capillary contains a red cell (*R*) and is lined by two endothelial cells (*en*) containing normal pinocytotic vesicles now known to be the site of certain detoxification enzyme systems (*p*). A normal interendothelial junction is noted at *J*. The widened portion of the interstitial compartment (*in*) contains a fibroblast (*fi*) showing little metabolic activity. (90,000×)

C, Shows a high magnification transmission electron micrograph of a widened interendothelial gap in the earliest stage of interstitial pulmonary edema. The lumen of the pulmonary capillary (*C*) is separated from the interstitial space (*in*) by the two endothelial cells (*EN*) making up the interendothelial junction or gap (small arrows). The measurements indicate that the narrowest point of this widened gap is approximately 100 Å wide (normal width = 40 Å). It is easy to visualize how serum albumin molecules (approximately 80 Å) could now pass freely through this open junction along with increased water and filtration solute. (500,000×)

ment[58] (Fig. 4, *B* and *C*). Under physiologic conditions, molecules larger than the interendothelial "pore" size, such as serum albumin (80 to 100 Å), can only sparsely pass through these narrow molecular sieves. The alveolar lining cells, also called Type I pneumocytes, are attached by tight junctions (zona occludens) (Fig. 5*C*). Unlike the endothelial gaps,

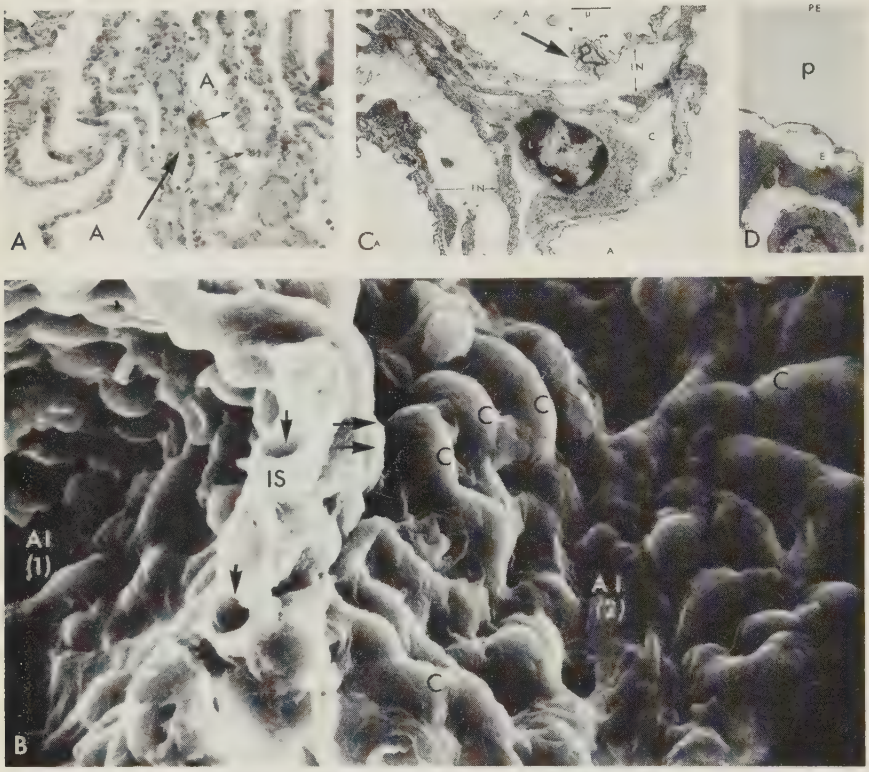

Figure 5. *A*, Light microscopical histopathology of pulmonary congestion with numerous crowded red blood cells causing dilatation of capillary lumina (large arrow) and tortuosity of other congested interalveolar septa (small arrow). Alveoli (*A*) show reduced volume due to sample being taken from base of lung. (300×)

B, Scanning electron micrograph demonstrating two congested alveoli (AL [1] at left and Al [2] at right) with an intervening interalveolar septum (*IS*) crossing vertically between them. The alveolar wall on the right shows the wormlike protrusion of tortuous congested pulmonary capillary segments (*C*) which bulge into the intraalveolar space. The parallel arrows point to the faint linear parallel grooves in one pulmonary capillary segment which has been produced by the compression of intraluminal red blood cells with the tension focally stretching the capillary walls. The alveolar surface is covered by smooth, thin Type I alveolar lining epithelium. The large arrow heads point to two capillaries in the interalveolar septum which have been cut cross-sectionally, thus revealing their internal luminal aspect. (5000×)

C, The ultrastructure of interstitial edema involving an interalveolar septum. The interstitium (*IN*) is widely dilated by edema fluid. An interstitial fibroblast (*F*) is compressed up against the Type I alveolar lining cell at the left. Alveoli (*A*), the capillary lumen (*C*), contains a circulating lymphocyte (*L*). The arrow points to a tight junction (zona occludens) of the Type I alveolar lining cells which in this instance is quite electron-dense (black) and tortuous. (5000×)

D, Ultrastructural perivascular edema. The vessel wall contains dark smooth muscle fibers (*M*) with a white, ill-defined, external elastic lamina (*E*). The periadventitial area is homogeneously filled with gray plastic protein (*P*) which has filtered through the leaking capillaries into the broad area of the interstitium (*PE*). (30,000×)

these interepithelial junctions are watertight seals preventing escape of interstitial fluid into alveoli.[58, 68] The resultant normal interstitial fluid filtrate is rapidly drained off by pulmonary lymphatics which are the "toilet" of the lung, and only if their tenfold normal drainage capacity is exceeded will interstitial edema result.[16, 63]

Capillary congestion or increased capillary luminal volume may stretch the interendothelial junction gaps and make them wider and more patent (Fig. 4*C*). Molecular "pore" size may also presumably increase due to still undefined biophysical factors affecting interendothelial gap permeability properties.[7] The role of pinocytotic vesicles in plasma filtrate transport is still unproven. There is structural and physiologic evidence to implicate abnormally widened endothelial junctions as a cause of increased capillary permeability and resultant markedly elevated transcapillary filtration rates of both plasma water, solute, and protein.[45, 66] The classic light microscopic picture of pulmonary congestion is the sole finding in what is interpreted as the earliest morphogenetic stage of ARI (Fig. 5*A*). Insights into the phenomenon of intraluminal distention with resultant interendothelial gap stretching or widening requires electron microscopic resolution (Fig. 4*C*). Pulmonary congestion with resultant intraluminal capillary distention is uniquely demonstrated by scanning electron microscopic (SEM) visualization (Fig. 5*B*). This tridimensional illustration of congestion, seen in an otherwise end-stage lung of ARI, is visualized as if the observer were within an alveolus utilizing a 10,000× powered telescope to examine the tortuous protuberant congested pulmonary capillaries protruding into the air sacs. This and additional ultrastructural observations vividly depict how pulmonary capillary endothelial junctions might stretch and actually widen during this earliest morphogenetic stage in the initiation of ARI[66, 68] (Fig. 4*C*). The immediately resultant interstitial edema can be demonstrated ultrastructurally but not light microscopically (Fig. 5*C*). Widening of the broader areas of the pulmonary interstitium surrounding vessels and bronchioles by protein-laden edema fluid then occurs (Fig. 5*D*). It is in these widest areas of the pulmonary interstitium, where hydrophylic mucopolysaccharide is most abundant and where interstitial pressures may be lowest, that the greatest accumulation of interstitial fluid ultimately occurs and may now be seen light microscopically. Edematously widened interlobular septa are the histopathologic counterparts of Kerley B lines seen on chest roentgenogram in patients with clinical interstitial edema[27] (Fig. 6*A*).

Since interstitial edema selectively spares and does not thicken the blood-air "membrane," there is no resultant interference with normal gas diffusion. Pulmonary interstitial edema may account for the accumulation of up to 500 ml of extravascular fluid retention before leakage occurs into alveoli.[63] Severe interstitial edema causes tachypnea by decreasing normal lung elasticity and compliance and by triggering off pressure-sensitive receptors that elicit a Hering-Breuer–like reflex arc response.[42] Premature distal airway closure due to interstitial edema may produce hypoxemia due to early ventilation-perfusion (V/Q) inequality[12, 48, 49, 64] (Fig. 9, *A* and *B*). In addition, the increase in pulmonary vascular resistance seen in ARI is attributable to perivascular edema in accordance

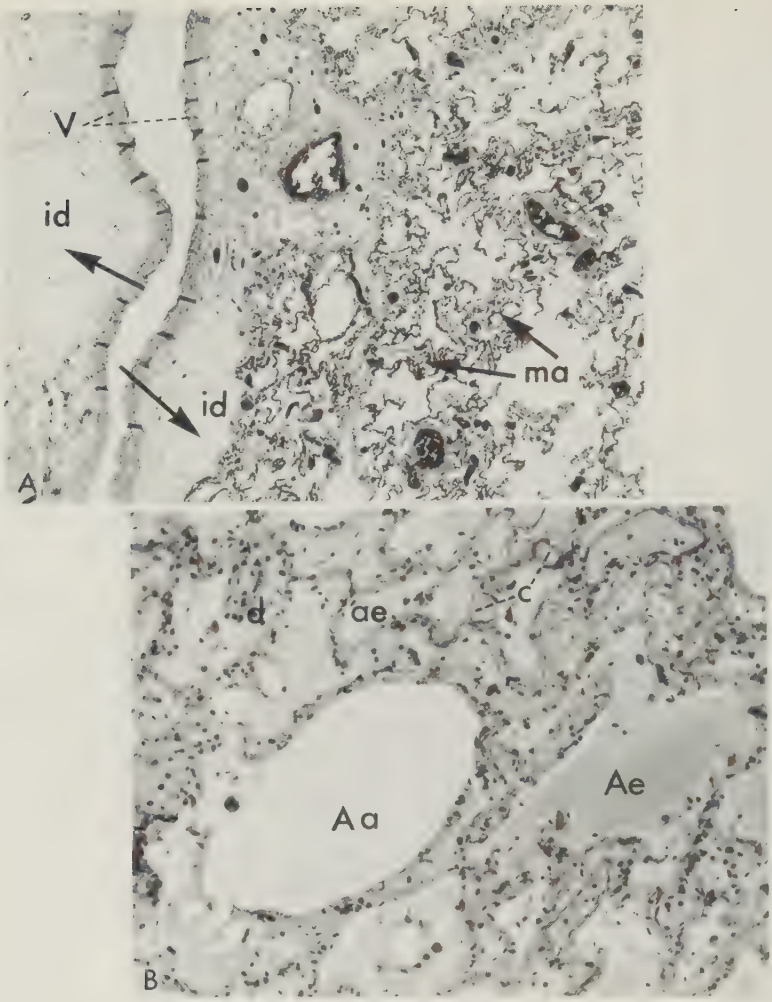

Figure 6. *A*, Light microscopical low magnification view of perivascular interstitial edema (*id*, with large arrow heads) running along the vertically cut vessel walls (*C*) within an interlobular septum (Kerley B line). The pulmonary capillaries in the right half of the photomicrograph are markedly congested. The alveoli show very considerable variation in their diameters or volumes. In some foci, the edematous alveoli have sufficiently reduced volumes such that the mistaken designation of microatelectasis could be applied (*ma*). The patient was a 40-year-old man dying rather quickly from fulminant pulmonary edema (lungs weighing 1700 gm) after acute massive myocardial infarction following abdominal surgery. One cannot identify stained edema fluid within the alveoli at this magnification because of the extremely low protein content in this rapidly progressing fatality due to cardiogenic pulmonary edema. (120×)

B, Classic histopathologic findings of homogeneous alveolar protein-laden edema fluid. The capillaries are congested (*C*). It is the protein in the edema fluid which stains and appears as homogeneous gray material within alveolar spaces which vary considerably in their diameters or volumes (*Ae*, large; *Ae*, small). A large alveolus filled with air rather than edema fluid is present (*Aa*). (Postmyocardial cardiogenic edema in a 57-year-old woman.) (300×)

with West's studies.[77] However, this point has been challenged by others.[63]

The exact mechanism(s) by which edema fluid finally traverses the intact continuous alveolar epithelial lining and gets into the alveolar spaces has still to be defined with certainty, although it is thought that interepithelial junctions may become permeable when sufficiently critical elevations in interstitial pressure are reached[66] (Fig. 7*A*).

Type I epithelial cells appear to be particularly vulnerable in many forms of acute interstitial injury.[3] In many diseases, such as inhalation of certain toxic fumes, it occurs as a primary and early alteration.[29] In other conditions, such as post-traumatic pulmonary insufficiency, it appears to be a secondary, nonspecific, and later reaction to interstitial injury.[69] In ARI, it is first detected as simple intracellular edema (see Fig. 7*A*). But with progression, degeneration and desquamation may ensue (Fig. 14*B*). Alveolar epithelial injury or degeneration obviously expedites exudation of fluid and protein into the alveoli (Fig. 13*B*).

Once the process of intraalveolar filling begins, the potential space for water-logging is remarkably increased, since functional residual capacity (lung gas volume at end-expiration) would theoretically allow for the accumulation of 3000 ml of fluid.[63] However, as will be seen later, the diameter and volume of edema-filled alveoli are reduced, thus limiting the intraalveolar fluid that can accumulate to the abnormally decreased FRC. Thus, even in massive pulmonary edema or wet lung, the extravascular volume of water rarely exceeds 1200 to 1500 ml (i.e., a total lung weight of 2000 gm).[71]

The histopathology of intraalveolar edema is hallmarked by eosinophilic pink-staining of the edema protein, since alveolar water per se cannot be visualized (see Fig. 6*B*). The postmortem severity of pulmonary edema and congestion or wet lung can only be quantitated by noting the degree of gross fluid transudation, determining the total lung weight, and, more electively, determining the so-called wet/dry lung weight ratio to determine percentage water increase in the parenchyma (see Fig. 1).

In fulminant rapidly progressive pulmonary edema, the typical foamy or frothy edema fluid that is expectorated arises from intermixture of inspired air with the fluid within larger bronchi and bronchioles where active airflow under pressure occurs, rather than in the alveolar ducts and the alveoli per se, where only passive gas diffusion takes place.[76] This is an important concept. Since, with unsupported (nonrespirator driven) breathing, air must passively and slowly diffuse rather than actively flow to the blood-air membrane of these distal acinar units, the presence of intraalveolar edema fluid represents a serious biophysical block to oxygen transfer because of the relatively low solubility of gas and to slow diffusivity through liquid. Thus, edematous alveoli are effectually nonventilated with regard to oxygen transfer.[12, 63, 75] Continued capillary perfusion without appreciable alveolar ventilation leads to markedly decreased ventilation perfusion (V/Q) or what is interpreted as "physiologic shunting" or so-called "physiologic atelectasis" (simply defined as nonventilated alveoli without any connotation indicating alveolar collapse). Very deep inspirations might theoretically allow for active gas flow down to

Figure 7. *See legend on opposite page.*

more distal acinar units, thus improving alveolar ventilation. However, the rapid shallow breathing seen early in these patients may serve by its bellows pumping action to increase pulmonary capillary blood volume and flow, but actually hinders alveolar ventilation because of decreased inspiratory pressures and resultant decreased active airway flow to peripheral acinar units. Mechanical ventilator support (large volumes and/or high pressure) as noted, will actively push aside alveolar edema fluid against the interalveolar septa, increase alveolar volume, increase alveolar air-blood membrane surface area, and thus instantly allow for increased oxygen diffusion through both air spaces and the blood-air barrier. Thus, there should be no mystery as to why continuous positive pressure breathing works with resultant increased functional residual capacity, increased compliance, and increased arterial oxygenation due to a marked increase in the V/Q ratio.[46]

Upon gazing at the simple histopathologic picture of protein-laden edema fluid in alveoli, other pathophysiologic insights may be gained (see Fig. 6*B*). First, the use of CPPB may cause active airflow into air sacs with the potential for resultant intraalveolar bubbles and foam. Secondly, the most severe degrees of increased capillary permeability will lead to exudation of the highest concentration of protein into alveoli. The size of the protein molecule that sieves through the capillary barrier will also be greater, resulting in fibrinogen (m.w. 400,000) leakage.[68, 70] Thus, in cardiogenic pulmonary edema, where interendothelial gaps may be only slightly widened, there is often a low concentration—low-molecular weight, protein-laden—edema fluid which can be rapidly reabsorbed from alveoli without any residuum soon after appropriate therapy decreases the increased capillary hydrostatic pressure (see Fig. 6*A*). However, as may be the case in noncardiogenic pulmonary edema, if the stimulus to increase capillary permeability is more injurious and prolonged, the resultant protein leakage will be more severe and protracted (Fig. 11). The concentration of protein in noncardiogenic forms of pulmonary edema may reach 6 gm per cent.[31] The patient might continue to have alveolar edema with highly concentrated protein containing fibrinogen which then polymerizes to form intraalveolar fibrin. The precipitated-

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Figure 7. *A*, The ultrastructure of early hyaline membrane formation and interstitial edema in human acute respiratory insufficiency. The dense electron-opaque inspissated protein aligning an intact Type I alveolar epithelial lining cell (*EP*) constitutes the transmission electron microscopic counterpart of hyaline membrane (*HM*). Periodicity indicative of fibrin is absent. The interstitium is markedly edematous (*EIN*) (note large double-headed arrows showing confines), separating the capillary endothelium (*EN*) from the Type I alveolar lining (*EP*) which are focally slightly injured and edematous (*EE*). Zonula occludens (epithelial junction) (*ZO*), capillary lumina (*C*), alveolus (*A*), red blood cells (*R*). Patient died 4 days after 90 per cent total body surface burn while on volume respirator support. (16,000×)

B, The light microscopic changes from the lower lobes of the patient depicted in 7*A*, showing widespread hyaline membrane formation throughout the entire parenchyma (*hm*). Occasional normal interalveolar septa are present for comparison (*is*). Intraalveolar edema is also present. The changes depicted were diffusely involving the lower lobe. The electron micrograph (7*A*) was taken from this area. (120×)

C, Uncomplicated light microscopic classic pulmonary edema (*E*), involving the alveoli in the upper lobes of the same patient as 7, *A* and *B*. Unlike the lower lobes, hyaline membranes are not present at all. Same magnification as 7*B*. (120×)

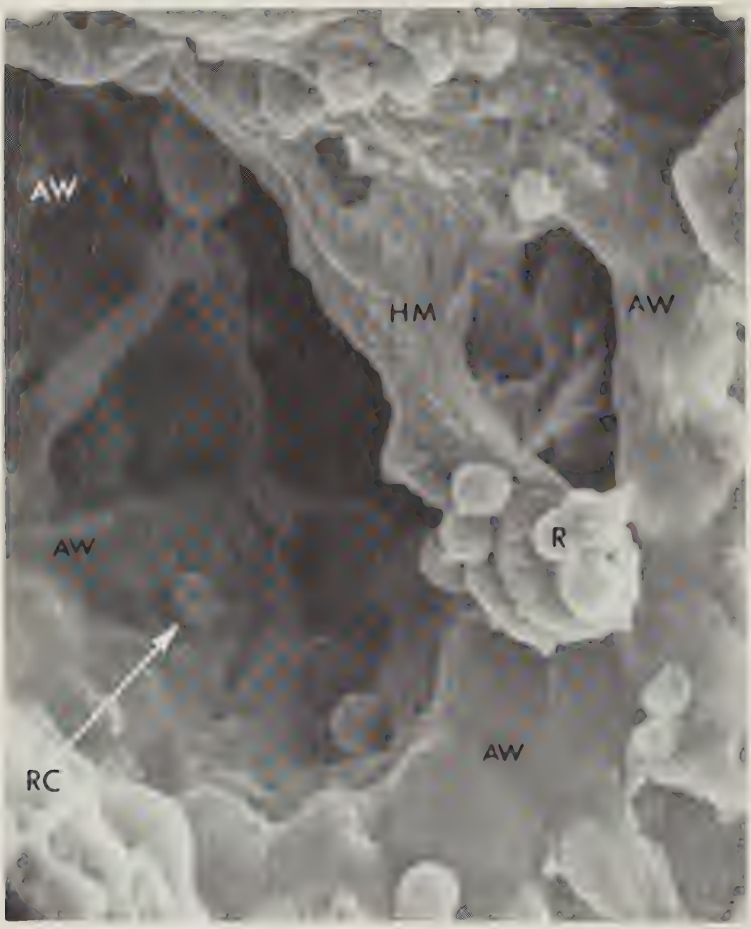

Figure 8. The scanning electron microscopic (tridimensional) picture of a hyaline membrane (*HM*) within a single alveolus. The inspissated coagulum of protein forms a spider web-like band attaching the right lateral and upper center aspects of the alveolar wall (*AW*). A donut-shaped red cell (*RC*) is lying on the bottom of the alveolus and the hyaline membrane has crenated red cells (*R*) attached to it. Note the intact smooth epithelium lining the alveolar walls. Thus, the hyaline membrane merely represents denatured inspissated and coagulated plasma protein which has leaked into the alveolus and which has been compressed up against the intact epithelial lining in this alveolar wall. Early morphogenetic stage of ventilator treated acute respiratory insufficiency. (10,000×)

coagulated alveolar plasma proteins can no longer be reabsorbed in the fluid state and therefore remain until they are enzymatically lysed or phagocytized. Such patients would be expected to have more prolonged refractory and more severe V/Q inequality, "physiologic shunting," and hypoxemia.

Morphogenesis and Pathophysiologic Significance of Hyaline Membrane Formation and Its Relationship to Modern Ventilatory Management

Hyaline membrane represents denatured inspissated plasma protein which is compressed against the interalveolar septal walls. Why is it that in certain variants of wet lung the end-stage pathologic picture is straightforward severe pulmonary edema, while in other severe variants, where increased capillary permeability is just as pronounced, a variable percentage of the intraalveolar protein is in some way transformed into widespread hyaline membrane? Since classic pathology texts[54] have traditionally emphasized the mysterious association of these unique membranes with either fatal influenzal viral pneumonitis or idiopathic fatal hyaline membrane disease of the newborn, clinical investigators tended to endow their emerging prominence in the setting of ARI that occurred after the mid-1960's with an aura of special specificity. The diagnosis of ARI was now dignified with the pathologic classification of interstitial pneumonitis with hyaline membrane formation or other descriptive phraseology, tending to overemphasize the histopathology's unique and special nomenclatural importance. The coexistence of high protein-laden edema in all these variants of wet lungs was often overlooked and pathogenesis was mistakenly linked to desquamation of Type I alveolar lining cells rather than to increased capillary permeability leading to intraalveolar edema protein deposition. The inconstant ultrastructural finding of fragments of necrotic desquamated Type I alveolar epithelial cells, in association with some hyaline membranes, could certainly not account for 99.9 per cent of their protein content. Thus, as previously indicated, lungs that were previously regarded as variants of severe pulmonary edema were now endowed with new appellations that bestowed an aura of specificity upon them. The era of Adult Respiratory Distress Syndrome, shock lung and post-traumatic pulmonary insufficiency came to being with presumed new disease entities that somehow had spontaneously arisen de novo. These fascinating historical aspects of emerging hyaline membrane formation in ARI will be further discussed later. However, since hyaline membrane formation contributes not only to altered structure which is of pathologic interest, but must also contribute to altered function and seemingly to unfavorable response to treatment with resultant negative prognostic implications, their significance warrants an understanding of their pathogenesis and morphogenesis.

From the presently available overall observations on the end-stage lung pathology resulting from increased capillary permeability, there would appear to be several independent and different factors responsible for hyaline membrane formation.

In certain variants of noncardiogenic "wet lung," hyaline membranes spontaneously form as a result of greatly increased capillary leakage with exudation of considerable amounts of high molecular weight protein, including fibrinogen. Fulminant Asian viral influenza pneumonia in the 1918 pandemic is a blatant example of such conditions. It is presumed that the leaking fibrinogen molecules tend to more readily polymerize at the immediate surface of the alveolar wall, giving rise to fibrin-laden hyaline membrane apposed to the interalveolar lining epithelium in patients who were never treated with ventilatory assistance or oxygen. There is evidence that in these primary spontaneous-forming hyaline membranes, pulmonary edema precedes the formation of the membranes[55] without superimposed oxygen toxicity. Hyaline membranes as seen commonly in ARI contain considerable serum albumin and globulin with lesser amounts of identifiable fibrin.[40, 69] In order to get drying, denaturation, coagulation, inspissation, and compression of these previously soluble serum proteins (of which polymerizable fibrinogen represents only a fraction thereof) against alveolar walls, there must be active air flow under pressure into the edema-laden air sacs. As already noted, active air flow under pressure through edematous alveoli does not appear to spontaneously occur in cardiogenic pulmonary edema, and since the condition is generally a self-limited disorder where the patient either rapidly gets well or dies, one would not expect to find dried inspissated hyaline membranes in the distal acinar-alveolar units. However, if air were now to actively flow under pressure through respiratory bronchioles and distal air sacs down to alveoli due to the use of volume respirators delivering air with increased tidal volumes, inspiratory (plateau) pressures and high oxygen concentrations, both the exerted active air flow and pressure, as well as the known drying effects of high oxygen concentrations would produce the critical set of conditions needed for the development of hyaline membrane formation, due to physical and biophysical (bioengineering) effects of the inspired gas on the protein-laden edema fluid.

To vividly support the contention that hyaline membrane may form as a simple variant of ventilator-treated pulmonary edema, the following case is cited. A burn patient died 3 days post-95 per cent total body surface involvement, receiving volume ventilator support with 40 per cent oxygen. The upper lobes as seen in Figure 7*A* show only pulmonary edema and congestion with no hyaline membrane formation, in striking contrast to the lower lobes seen in Figure 7*B*, which show widespread hyaline membrane formation and, therefore, the classic histopathologic picture of progressive ARI. Such cases showing such a regional dichotomy are indeed rare but, nonetheless, serve to confirm the fact that even within the same patient's lungs, hyaline membrane formation, in its least complicated form, may only be an extension of severe pulmonary edema and congestion, without implicating other superimposed etiologic or pathogenetic factors. The differentials in capillary filtration pressure and active air flow pressure, with alveolar volume distension between upper and lower lobes, might be theoretically implicated to explain the observed findings.

Finally, the third obvious cause of hyaline membrane formation in ARI is true oxygen toxicity.[9, 39] It is now well proven that the latter causes marked ultrastructural endothelial damage in both man and animals, leading to high molecular weight protein exudation, including fibrinogen.[18, 24, 25, 39] Oxygen toxicity in man has become viewed as a primary form of acute interstitial pneumonitis with marked capillary damage equivalent to fulminant influenza pneumonia.[29] The hyaline membranes found in humans have thus been attributed to spontaneous primary formation as seen in untreated fatal influenza. However, paradoxically, hyaline membranes have not been found in experimental oxygen toxicity in animals,[24, 25] including primates (the latter being an excellent model), where oxygen is not delivered by mechanical ventilators. Thus, even this third and iatrogenic cause of increased capillary permeability in patients with ARI may require the contribution of the mechanical ventilator to account for the aforementioned discrepancy and case variations with regard to the existence and/or severity of hyaline membrane formation.

Historical Changes in the Pathology of ARI in the Last Century Accounting For Confusion Concerning Pathogenesis and Clinical-Pathologic Nomenclature

In Moon's classic studies of fatal shock following trauma, burns, poisoning, infections, heat stroke, abdominal emergencies (intestinal obstruction, infarction, pancreatitis, etc.) during World War II, severe pulmonary edema was present but hyaline membranes were absent.[35] Similar studies by others, dating back to both world wars, also failed to reveal hyaline membranes in the wet lungs found in patients dying in the early phases of clinical settings where they would now be monitored and treated in Intensive Care Units for early ARI.[6, 19, 32, 38] Pathologists were very tuned into the issue of hyaline membrane formation due to their dread experience with it in the 1918 influenza pandemic and thus they surely would not have failed to describe this important histologic finding if it were present.

This point is more than one of just historical interest because it is an observation of perhaps monumental relevance with respect to the very important issue concerning the earliest stage in the pathogenesis of ARI (still an *undetermined* and controversial point, where experimental models have been of little value). It also has great bearing on the changing pathology and the altered biology of the disease process of ARI that has been noted during the past few decades. Thus, to repeat, mysterious variants of ARI of the mid- to late 1960's (so-called shock lung, adult respiratory distress syndrome, etc.) of presumed unknown pathogenesis, revealing striking end-stage pathology suggesting a distinctive interstitial pneumonitis, were nothing more than cases of massive pulmonary edema and congestion without any other major findings, such as atelectasis, when the patient died in the very early stages of development or morphogenesis without iatrogenic intervention. This is important contributory historical evidence to indicate that indeed pulmonary capillary permeability was the first and paramount pathogenetic factor involved in the biologic course of progressive ARI; and it is difficult to think of legiti-

mate reasons not to extrapolate those well documented findings to our present understanding of the development, pathogenesis and progression of the disease process as it now exists. There can be no doubt that the pathology of ARI, with diffuse hyaline membrane formation as the modern pathologist now knows it, had its advent at precisely the same time that blood gases became routinely available for monitoring, and Pulmonary Intensive Care Units were first established. This era specifically dates back to around 1963. The author was in an unique position to relate the historical differences in pathology seen in the pre- and postintensive pulmonary care era since he was the pathologist at the U.S. Army Surgical Research Unit (Institute), Burn and Trauma Section (U.S.A.S.R.U.), from 1961 to 1963, when both routine blood gas determinations and routine volume respirator support were just being introduced. Prior to 1961, hyaline membrane formation and the modern-day pathology of so-called adult respiratory distress syndrome was indeed a very isolated, rare finding. In the 90 burn cases autopsied by this observer prior to 1963, only one case fell into this category.[67] On the other hand, severe pulmonary edema with lungs weighing over 1500 to 2000 gm were seen in over one-third of all patients dying from thermal burn injury, and those who died early in their resuscitative period with ARI consistently showed massive pulmonary edema and congestion that was in no way pathologically distinctive.[67] Those dying with severe pulmonary edema and congestion in association with the late complication of fulminant sepsis showed precisely the same findings.[67]

However, blood gas monitoring with aggressive machine-controlled ventilatory support became routine in late 1963, and in the 2 years that followed there was a very marked increase in hyaline membrane formation with the modern altered pathology of ARI, without any change in epidemiologic variables.[17] At a Surgeon General's Symposium, in 1966, on the meaningfulness of hyaline membranes in burn patients with ARI, assertions were made that the new pathology with distinctive ubiquitous hyaline membranes represented a heretofore undescribed or undiagnosed entity of so-called "shock lung." Since the population of the burn and trauma patients seen at U.S.A.S.R.U. had not changed an iota, it appeared more logical that the altered pathology was due to altered treatment rather than to the discovery of an entirely new disease entity. This view was sharply criticized by well known clinicians who had not had the opportunity to confront the pulmonary pathology of trauma on a daily basis during this transitional period. The National Academy of Science Symposium on Effects of Non-thoracic Trauma, in 1968,[51] ultimately legitimatized the presumed entities of so-called post-traumatic pulmonary insufficiency or adult respiratory distress syndrome, which has since led to a spate of over 1000 articles on the subject, with a disproportionately small increase in undisputable facts on pathogenesis.

As the Vietnam War progressed into the late 1960's and as aggressive pulmonary intensive care in general hospitals became even more ubiquitous, the clinical and pathologic picture of acute respiratory insufficiency with hyaline membranes became commonplace, while the original virginal and pristine simple pathology of massive fatal pulmonary edema and

congestion became increasingly rare. How much of the advent of interstitial pneumonitis with hyaline membranes in ARI during this historical transitional period was due to (1) ventilator effect on existent protein-laden edema fluid, (2) the prolongation of life with prolongation of the period of increased capillary permeability with greater accumulation of denatured intraalveolar protein and a greater likelihood for inspissation and compression of this protein with the passage of time, and (3) the actual toxicity of oxygen, cannot be dissected out or quantified. There can be little doubt that all three factors were involved and that the birth of so-called ARDS, with its classic pathologic picture, appears to have been nothing more than the iatrogenic effect of modern medicine on the biology of a disease (noncardiogenic pulmonary edema) that was as old as man himself.

Figure 9*A* shows the histopathologic changes in a 19-year-old man dying 5 days post-trauma (motorcycle accident) with progressive ARI. There is severe pulmonary edema and congestion with widespread hyaline membrane formation, focal intraalveolar hemorrhage, and early cuboidal lining cell (granular-pneumocytic) hyperplasia. These are the

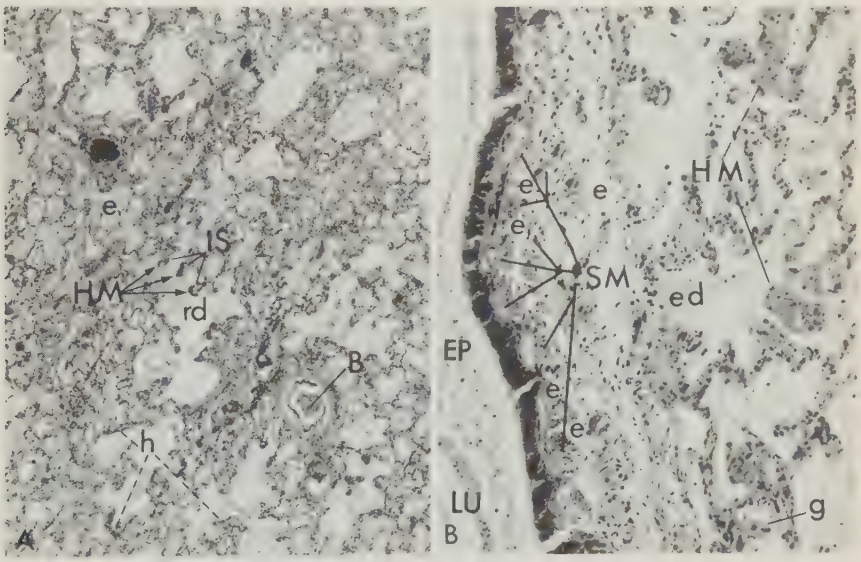

Figure 9. *A*, The classic low magnification histopathologic picture of treated progressive acute respiratory insufficiency. There is widespread intraalveolar edema (*e*), hyaline membrane formation (*h*), and focal intraalveolar cellular debris. The small arrows point to hyaline membranes (*HM*) which have formed at the tip of interalveolar septae (*is*) projecting into a respiratory duct (*rd*). The center of a bronchiole (*B*) which is markedly reduced in caliber contains protein debris within its lumen. (30×)

B, Light microscopic demonstration of severe edema and congestion of the mucosa. The smooth muscle bundles (*SM*) subjacent to the surface epithelium (*EP*) are markedly disrupted by intercellular edema (*e*), unquestionably resulting in contractile dysfunction of the airway. The alveoli to the right show intraalveolar edema (*ed*) congestion, focal hyaline membrane formation (*HM*), and focal early granular pneumocytic hyperplasia (*g*). These latter findings decrease the elasticity of the parenchyma and, therefore, decrease the normal tethering action on the bronchial wall resulting in end-expiratory premature closure. Bronchiole lumen (*LU*). (300×)

classic findings of treated ARI. There is prominent localization of hyaline membranes at the innermost luminal aspect of the respiratory bronchioles and alveolar ducts. This is often an early and consistent localization in ARI. The inner aspects of the respiratory bronchioles would represent the proximal site at which inspiratory distal airway flow rates would be maximal in gas-exchanging or alveolar-containing acinar units. It is where inspired oxygen concentrations are highest and pulmonary capillary-derived water vapor pressure lowest—the very sites where air pressure and drying of transuded plasma protein might first take place. The inherent rigidity of denatured protein of hyaline membranes in respiratory bronchioles might have a serious physiologic consequence since they would tend to decrease the elasticity and compliance of distal acinar airways, and possibly increase their airflow resistance by decreasing their luminal caliber. The membranes' rigidity might also interfere with normal distal airway smooth muscle contraction and relaxation, since they are firmly affixed to respiratory bronchiolar and alveolar duct muscle bundles (see Figs. 2 and 9*A*). The intraalveolar hyaline membranes, in addition to protein debris, desquamated alveolar lining cells, intraalveolar macrophages, extravasated red blood cells, and already existent edema fluid, would contribute further to the already poor alveolar ventilation and low V/Q ratio. The restrictive hyaline membranes and intraalveolar cellular debris must indeed also contribute to abnormally altered lung volume function parameters, including the decreased FRC. Nonetheless, any purist physiologist who studied these totally altered distal airways and alveoli might shudder before attempting to say what precisely he were measuring when using either the helium or oxygen washout test used for determination of FRC under more normal structural conditions.[76]

Additional Pathologic Alterations in Relation to Premature Airway Closure, Closing Volume, and Distal Airway Resistance

The terminal bronchioles in ARI often appear of decreased luminal caliber, i.e., partly collapsed (see Fig. 9*A*). The patency of terminal bronchioles, particularly in end-expiration, is entirely dependent upon the normal tethering action of the surrounding elastic interalveolar septa.[48, 49, 76] Distal airway collapse due to the loss of such elastic tethering action in end-expiration is well known to students of emphysema.[48] There can be little doubt that the normal peribronchiolar elastic retraction of parenchyma which maintains airway patency in expiration is markedly decreased due to (1) interstitial edema directly affecting interalveolar septal stretching (compliance), (2) cuboidal lining cell hyperplasia (granular pneumocytic hyperplasia) which also decreases alveolar elasticity, and (3) the presence of rigid restrictive hyaline membranes. Peribronchiolar edema is also contributory (Fig. 9*B*). Thus, increased terminal bronchiolar airway resistance and increased end-expiratory closing volume results. Bronchiolar lumina may be filled with proteinaceous debris and red blood cells, as noted in Figure 9*A*. The tridimensional scanning electron microscopic visualization of a narrowed alveolar duct filled with red cells and coagulated protein and fibrin gives striking testimony to the distal airway problems that may be present in severe ARI (Fig. 10).

Mucosal edema of small bronchi and bronchioles may actually disrupt smooth muscle bundle units and structural integrity and interfere with normal function (Figs. 9*B* and 10). The observed pathology would adequately explain the clinical need for maintaining increased positive end-expiratory pressure to prevent terminal bronchiolar airway closure. It should also be clear from the progressive pathology which eventuates in decreased alveolar volume and rigidity of distal acinar units, that if sufficient volume expansion of acinar alveolar units by a volume respirator were to abruptly cease, catastrophic changes in distal airway and alveolar-acinar units would result. The continually progressing interstitial pneumonitis becomes an increasingly restrictive distal acinar pulmonary disorder which leads to significantly decreased blood-air barrier surface area. Maintaining high pressure ventilatory breathing counterbalances this restrictive propensity. Finally, on or about the 6th day after injury and treatment, fibroblastic ingrowth into the hyaline membrane may occur, producing further restrictive physiologic problems as fibrosis begins and increases (Fig. 12).

Noncardiogenic Forms of Pulmonary Edema Leading to the Same Clinicopathologic Picture of Acute Respiratory Insufficiency

Figure 11 represents the histopathologic picture seen in aspiration pneumonitis or so-called Mendelsohn's syndrome, where there has been aspiration of gastric hydrochloric acid (HCl). This chemical pneumonitis

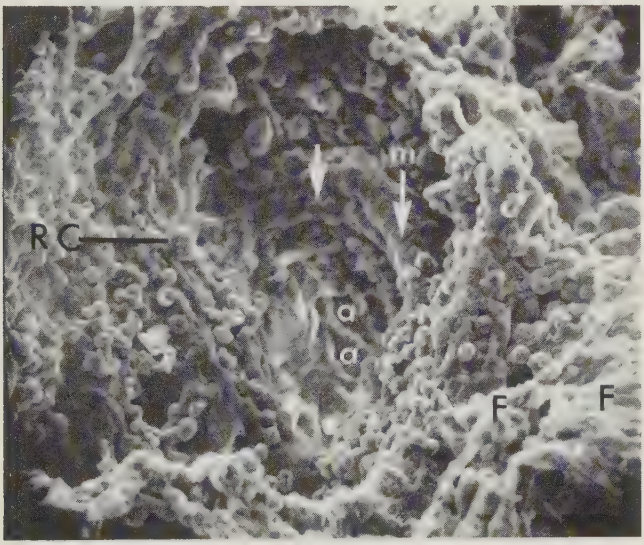

Figure 10. Scanning electron micrograph (tridimensional view) of a respiratory bronchiole looking down through an alveolar duct into distal "cavernous" alveoli (*a*). The white arrow points to what are probably bundles of smooth muscle (*m*) in the alveolar duct. Numerous red cells (*RC*) and coagulated fibrin protein strands (*F*) cover the proximal portion of the respiratory bronchiole in this patient dying with progressive ARI. The degree of distal airway dysfunction in ARI can more easily be appreciated by this tridimensional depiction of the intrinsic pathology. (2500×)

has unfortunately been categorized under the all-inclusive label of ARDS.[53] There are numerous types of toxic interstitial pneumonitides which lead to the same pathologic and pathophysiologic pictures of ARI.[29] All are due to marked capillary endothelial damage and, if the patient dies in the earliest stages, prior to treatment, massive pulmonary edema is the sole pathology. Later, alterations are those of superimposed interstitial pneumonitis with hyaline membrane formation and fibrosis (see Fig. 11).

Ultrastructurally Detectable Endothelial Damage As a Cause For Refractory Capillary Leakage

Toxic injury to pulmonary capillary endothelium may cause recognizable ultrastructural change, as for example in oxygen toxicity.[18, 24, 25] Figure 12*B* shows the ultrastructural changes seen in a patient who died 7 days post-traumatic injury, who had received ventilatory support with increasing toxic concentrations (> 70 per cent) of oxygen. Widespread endothelial damage is present. Thus, increased permeability in relation to widened interendothelial junctions is no longer the sole, relatively reversible variable responsible for capillary leakage. In our own experience, edematous and injured endothelial cells are commonly found in late stages of progressive pulmonary insufficiency during which the patient has become refractory to treatment (Figs. 12*B* and 14*A* and *B*). Because current management, including positive pressure ventilation, diuretics, fluid restriction, etc., would no longer alter the pathophysiology of these structurally and metabolically damaged freely-leaking capillaries, the pathologic basis for fatal progression in such patients becomes obvious.

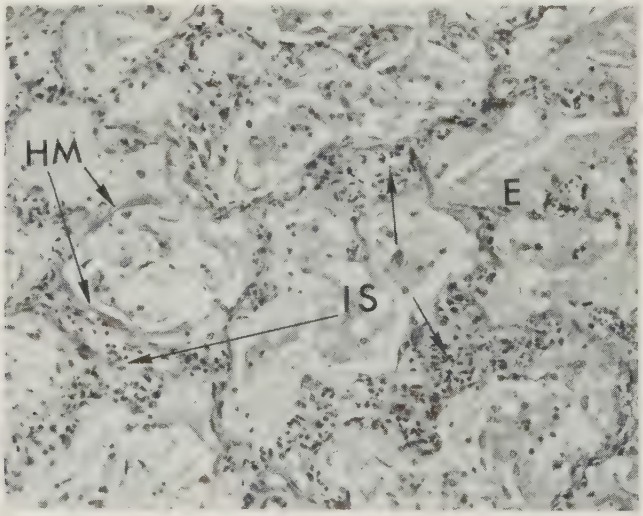

Figure 11. Light microscopic picture of gastric hydrochloric acid aspiration in an alcoholic patient. There is interstitial edema and lymphocytic infiltration of interalveolar septa (*IS*). The alveoli contain densely stained high-protein edema fluid (*E*) and focal hyaline membrane (*HM*). This form of chemical interstitial pneumonitis is indistinguishable from that seen in the developing stage of post-traumatic ARI seen at about 5 days postinjury. (300×)

Figure 12. *A*, Upper right corner: Electron micrograph reveals a leukocyte microthrombus aggregate (three adherent cells) within a pulmonary capillary found in a precardiopulmonary bypass control specimen. Such ultrastructural microthrombi are not often found in cases of progressive ARI in humans as opposed to dogs. Leukocyte nuclei (*N*) and granules (*G*). Endothelial cell (*EN*). (10,000×)

B, Center: Electron micrograph showing two fibroblasts (*FI*) containing numerous parallel stacks of ribosome-studded cisternae called rough endoplasmic reticulum (*RER*). The latter is the organelle responsible for the manufacture of procollagen, which has not yet been extracellularly laid down. Therefore, these fibroblasts are gearing up in the early stages of interstitial fibrogenesis. The capillary at the left center contains two endothelial lining (*EN*) cells. The left gray one is relatively normal, with slightly increased pinocytotic activity (*P*). The right endothelial cell shows marked swelling and edema (*e*), with loss of pinocytotic activity, but the cell still contains normal mitochondria (*M*), thus indicating potential reversibility of this form of endothelial damage. An arrow points to a site of cytoplasmic disruption of the injured endothelial cell, which may represent the point of rupture from which the red blood cell (*R*) has found its way into this widened edematous portion of the interstitial compartment. The capillary lumen (*CAP*) contains gray plasma. ARI 6 days post-traumatic injury. (20,000×)

C, Lower left corner: Light microscopic hyaline membranes (*HM*) in apposition to interalveolar septa (*IS*). The latter show fibroblastic proliferation (*F*) and there is early fibroblastic ingrowth into the hyaline membrane (see arrows). (480×)

On a theoretical basis, only membrane oxygenator extracorporeal support might allow life to continue long enough for reversal of endothelial edema and even allow for endothelial regeneration where irreversible endothelial injury has occurred.[81] Evidence for such reparative endothelial regeneration in ARI is depicted in Figure 17. However, even membrane oxygenator resting of the damaged lungs would not facilitate the removal of the exuded, coagulated interstitial and intraalveolar protein which serves as the nidus for irreversible fibroblastic collagen deposition and fibrosis. Thus, the ultimate safe answer to the cure of refractory fatal ARI might rest on the development of specific pharmacologic therapy which is unequivocally effectual in diminishing capillary leakage from injured endothelium. Steroids have not clearly appeared to be the answer to the problem.[78]

When endothelial edema and early injury occurs, there is a marked decrease in the number of pinocytotic vesicles (see Fig. 12*A*). It is now known that pulmonary capillary pinocytotic vesicles are the site of specific enzymatic localization for the metabolism and detoxification of vasoactive substances including kinins, prostaglandins, etc. Thus, the lung is an enormously important metabolic organ whose endothelial pinocytotic vesicles may prove, in their own right, to be as important as hepatocytes in detoxification functions.[56] The role of vasoactive amine metabolism in the pathogenesis of ARI and other diseases is an exceedingly important area of research; however, because there is little firm evidence for what these agents do or do not do in human diseases, as opposed to animal models, it is beyond the scope of this paper to speculate on this problem. Nonetheless, it would now appear that the failing lung not only is a problem in relation to gas exchange, but also in relation to both local pulmonary and systemic pharmacologic-metabolic detoxification, processes which may secondarily affect both lung and systemic further deterioration.

Microthrombi As a Possible Cause of Capillary Injury—A Much Accepted But Not Well Founded Conclusion

Many etiologic and pathogenetic factors have been implicated for direct capillary damage in progressive ARI, almost wholly on the basis of animal experimentation and theoretics. Hypoxic damage has been implicated in the past, but recent evidence suggests that hypoxia does not alter pulmonary capillary permeability.[74] Primary importance has been attributed to the role of degranulating leukocytic microthrombi.[78, 79] The leukocyte microthrombus demonstrated in Figure 12*A* was taken from a normal control biopsy prior to the use of a bubble oxygenator cardiopulmonary bypass procedure. Such pulmonary microthrombi may increase slightly after prolonged lung manipulation during cardiothoracic surgery, but our own studies do not confirm the pathogenetic importance of alleged appreciable numbers of leukocyte aggregates in causing any harm to lung in humans, in contradistinction to animals.[79] Our own ultrastructural studies of the lungs of ARI and a critical and fair review of the entire literature reveal no firm documentation for their appreciable presence

and importance in the pathogenesis of human ARI. Perhaps the only qualification required is that septic patients with peripheral leukocytosis will show increased numbers of leukocytes in pulmonary capillaries, as well as certain other systemic capillary beds. There is no proof existent that this finding is anything more than a secondary reflection of sepsis without primary pathogenetic significance. The thesis of leukocytic lysosomal injury to endothelium has been prematurely accepted in the surgical literature as fact, probably because it is so appealing, but not because it is proven. Aside from the inability for some investigators to demonstrate their presence in ARI, there are valid reasons to question the validity of the thesis. Intracapillary and intraalveolar neutrophils are rampant in pneumococcal pneumonia. Yet, the natural biology is one of resolution without pathologic residuum rather than pulmonary autodigestion. Prodigious numbers of lysosome-containing leukocytes with microaggregates may be present within pulmonary capillaries of chronic myelogenous leukemia and pulmonary dysfunction does not occur.

Platelet and fibrin microthrombi also have been strongly implicated in the pathogenesis of ARI.[21, 65] Although disseminated intravascular coagulation is seen in association with ARI, other pathogenetic factors such as sepsis are usually also operative. Identifiable and appreciable pulmonary microthrombi in human ARI are rare or nonexistent in our and other investigators' studies.[2, 57] That they are not found because of the proffered reasoning that they are lysed, with their toxic liberated products producing the capillary damage, is becoming more difficult to accept in a process such as DIC which has a repetitive cyclic continuum. It is improbable that they would not be found in one of their cyclic intact phases in the study of human lungs with ARI if they were quantitatively and, therefore, pathogenetically important. Patients undergoing total body excision of large burns at the U.S.A.S.R.U. used remarkable amounts of old bank blood without the use of filters. In one large series receiving more than 7000 ml of old bank blood (mean of 14,000 ml), the differential incidence of observed autopsy microthrombi and the presence of clinical pulmonary symptomatology were insignificant and represented a statistical scattergram when any correlation was attempted with a group of patients receiving less than 1000 ml (mean 350 ml).[71]

Despite widespread acceptance of the pathogenetic role of microthrombi in ARI, it is not clear that well controlled human studies have documented the unquestioned pathophysiologic and clinical importance of sludge, platelet, or fibrin thromboemboli in the pulmonary microcirculation, albeit the appeal of such a postulate is tremendously logical. The lung serves as a filter for everything that is present and forms within the blood stream. It is becoming increasingly clear that this gas-exchanging sponge is indeed a very much more rugged particle-detoxification, organ filter than has been previously appreciated.

Measures to reduce sludge, leukocyte, platelet, and fibrin microthrombi are commendable and reasonable, but again, there are insufficient scientific data to support the wide consensus and conclusion in the surgical literature that such pulmonary microcirculatory aggregate filtration is of significant value in reducing the incidence of ARI.

Acute Respiratory Insufficiency and Sepsis

There is little clinical doubt that human septic shock, in ways still yet undefined, causes a refractory form of increased pulmonary capillary permeability often leading to fatal ARI. Clowes has amply demonstrated that when intrathoracic sepsis of widespread pneumonia becomes a complicating factor in already existent ARI, not only is the patient unsalvageable because of the known lethal systemic effects of sepsis, but inflammatory exudate within alveoli leads to further decreased ventilation-perfusion ratios (increased physiologic shunting) and a more rapidly fatal hypoxemic outcome.[10] Septic shock presently accounts for the majority of cases of ARI seen in large general hospital populations, particularly on medical wards. However, how various bacteria and bacterial products may truly injure the pulmonary and systemic microcirculation in human sepsis is still very much a totally bewildering problem. A review of the experimental literature[11] on this complex and controversial subject is beyond the scope and relevance of this article.

The Probably Irreversible and Potentially Lethal Problem of Interstitial Fibrogenesis (Fibrosis) in Progressive Acute Respiratory Insufficiency

The appearance of fibroblasts gearing up on day 6 postinjury to lay down interstitial collagen in the early process of fibrogenesis as a cellular reaction to interstitial injury in ARI is depicted in Figure 12*B*. Although the dynamic metabolic turnover of interstitial collagen and elastin has been the subject of a recent review,[22] for practical working purposes, interstitial fibrosis is presently considered an irreversible process. It is the lethal determining cellular process in chronic stages of interstitial injury. There is evidence that prolonged interstitial edema may be fibrogenic, and mitral stenosis with chronic passive congestion and interstitial edema is the best known, simple human model for this process.[29] In conditions characterized by high protein interstitial edema,[22] fibrogenesis appears to progress more rapidly. Thus, in the setting of prolonged increased capillary permeability, which does not respond to conservative management and in which there is the added component of protracted oxygen toxicity, progressive interstitial fibrosis invariably results. Treated progressive ARI of 3 weeks' duration may show far advanced interstitial fibrosis indistinguishable from Hamman-Rich syndrome (idiopathic interstitial fibrosis). It is probable that most patients who survive a week probably develop at least a focal or slight component of interstitial fibrosis of questionable clinical significance. Fibroblastic proliferation beginning in a hyaline membrane in a patient dying 6 days postinjury is demonstrated in Figure 12*C*. Although steroids have often been empirically used in pulmonary medicine to attempt prevention of interstitial fibrosis in a variety of lung disorders, controlled studies indicating their unquestioned efficacy are difficult to perform and are disappointingly scarce. Thus, in the setting of ARI, where infection is the most common lethal terminating event, the use of steroids for the prevention of interstitial fibrosis and other forms of pulmonary cellular injury repre-

sents a known risk, but a still yet unproven asset in the management of most patients. Although certain variants of ARI, such as aspiration or inhalation of chemical fluids or fumes, seem empirically to respond sometimes dramatically to the use of large doses of corticosteroids, the efficacy of steroids in fat embolization, although accepted by many, is still a difficult fact to prove (Fig. 13, *A* and *B*). The ultrastructural pathology of human fat embolization is illustrated in Figure 13*B*. The patient died 4 days post-traumatic injury with massive fat embolization and progressive ARI. A typical fat embolus indistinguishable from that seen in adipose tissue (rather than fat which seems to be an aggregation of chylo-microns) is noted. The endothelial layer shows a spectrum of recognizable viable cells and degenerating endothelial cells. The molecular pathology involved in capillary endothelial damage is unknown, but this electron micrograph documents the existence of such damage, in contradistinction to statements in the older human pathology literature that fat emboli do not directly cause pulmonary microcirculatory damage but produce dyspnea due to microembolic effects on the medullary respiratory center.

The Phenomenon of Focal Peripheral Endothelial and Epithelial Degeneration, a Reversible Cellular Reaction to Injury

Figure 14*A* represents a stage of injury in a case of vigorously resuscitated hemorrhagic shock with superimposed volume ventilator support with toxic concentrations of oxygen. In this electron micrograph one can follow a relatively normal endothelial cell, with perfectly intact mitochondria and pinocytotic activity, to a point most distal from its nucleus, where there is an abrupt cessation of pinocytotic activity with associated edematous swelling of the cytoplasm. In Figure 14*B* the same type of focal endothelial degeneration is noted at the junctions of two endothelial cells which are farthest from the nucleus. Weibel has also described focal peripheral cytoplasmic injury in the alveolar Type I epithelial cell, which is equally as long as the capillary endothelial cells and also has much of its cytoplasm quite distant from the metabolic machinery of the nucleus and perinuclear organelles.[3] Because the lung (interalveolar septa) is somewhat unique in that its two major cell types are extremely elongate and thin, this type of heretofore virtually unknown pathobiologic reaction to injury is a matter of considerable importance in pulmonary disease. That is, in both pulmonary endothelial and Type I alveolar epithelial lining cells, which constitute the blood-air barrier and the confines of the interstitium, the cyotplasm most peripheral from the nucleus is most prone to injury. The practical meaningfulness of this phenomenon is that if the damaged cells do not undergo further injury and retain their polyribosomal capability of protein synthesis for internal cellular repair, the peripheral portion of the cell may spontaneously regenerate itself. That is, cellular regeneration de novo from mitotic activity is not necessary for reconstitution and repair. Until such peripheral repair (cytoplasmic regeneration) takes place, it is presumed that the peripheral focal edema with loss of pinocytotic activity, may alter both endothelial and epithelial cellular function.

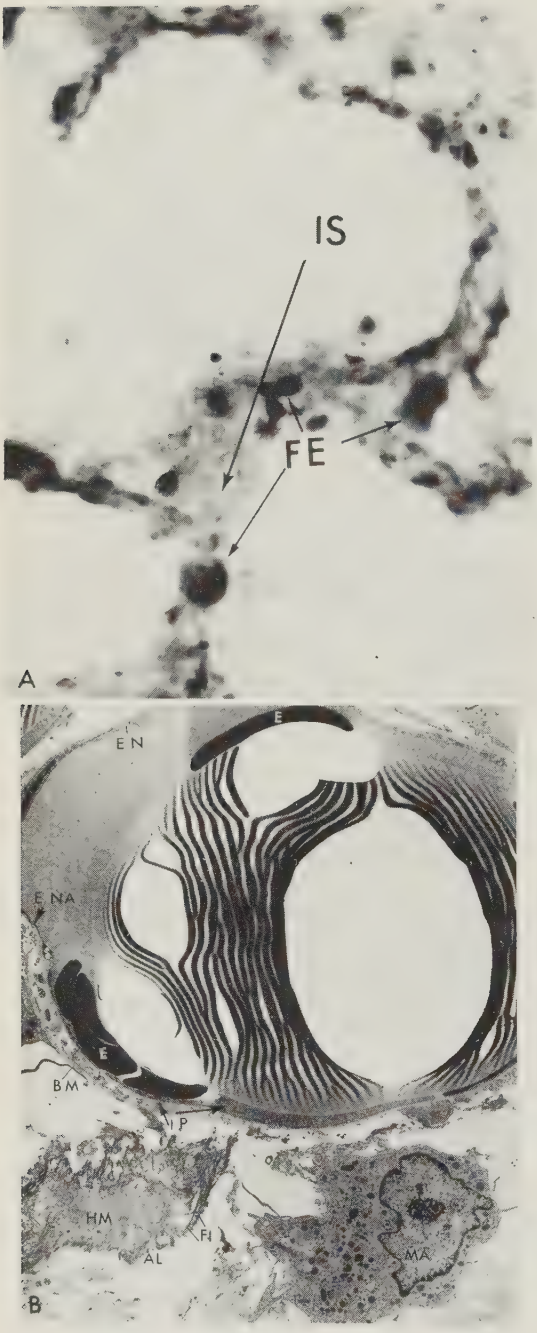

Figure 13. *A*, Shows the light microscopic-histochemical picture of massive fat embolization stained with Sudan fat stain. Fat emboli in capillaries are seen as dark globules scattered throughout the interalveolar septa (*IS*). (300 ×)

B, The ultrastructure of fat embolization in the same patient as 13*A*, 4 days post-trauma and multiple fractures. A fat embolus is identified by its white clear spaces with interspersed black broad wavy parallel lines. Fragmented erythrocytes (*E*) and the fat globules compress dense inspissated plasma (*IP*). At the left lower aspect of the capillary, a very electron-dense attenuated damaged endothelial cell (*ENA*) shows loss of normal pinocytotic activity. At the upper left is an endothelial cell that is relatively intact and shows minimal focal edema but no clear evidence of degeneration. The basement membrane (*BM*) is somewhat frayed and the alveolar lining cells are desquamated. A coagulum of protein within the alveolus (*AL*) represents the ultrastructural equivalent of hyaline membrane (*HM*) containing inspissated protein, fibrin (*FI*), and cellular debris. A pulmonary macrophage (*MA*) is present. (30,000×)

Figure 14. *A*, Upper left frame: Ultrastructural documentation of focal (reversible) capillary endothelial injury. The capillary segment to the right (large arrowhead) shows perfectly normal ultrastructure with numerous normal pinocytotic vesicles (*PV*) and normal mitochondria (*M*). As one tracks the endothelial cell down to the bottom left portion of the micrograph there is a rather sudden disappearance of pinocytotic activity with marked cytoplasmic edema (*E*), indicating focal cytoplasmic injury. The capillary lumen (*CA*) contains gray plasma protein. Interstitial lymphocyte (*L*) and fibroblast (*FI*). (30,000×)

B, The larger electron micrograph (center right) shows focal endothelial injury (swelling) with edema and loss of pinocytotic activity (*E*) at points most distant from the nucleus (*N*) of the two joining endothelial cells (*EN 1* and 2). Interendothelial junction (*J*). The subjacent basement membrane (*BM*) is somewhat edematous and frayed and there is loss of integrity of the normal alveolar epithelial lining cells, although small intact epithelial segments still remain (*EPs*). Endothelial cell cytoplasm (*CY*) and nucleus (*N*). (23,000×)

Injury, Degeneration, Desquamation, and Reconstitution of the Alveolar Type I Epithelial Cell

The attenuate, elongate squamous alveolar (Type I) lining cell is quite vulnerable to injury. It has no apparent mitotic capability. If injury is of the focal peripheral type as previously described, autonomous cytoplasmic regeneration is possible. However, if the entire epithelial cell is irreversibly injured, which often happens to a greater or lesser degree in many forms of interstitial injury, including progressive ARI, the alveolar Type I cell desquamates.[29] There is then a naked exposed basement membrane (see Fig. 14*B*). How does the alveolar epithelial barrier reconstitute itself? Figure 14*B* shows such an ultrastructural stage in the morphogenesis of ARI where the basement membrane is somewhat frayed and is denuded of its normal epithelial lining cells. Focal endothelial edema is also present in the contiguous capillary. In such a situation, edema fluid which has filtered through the endothelial barrier can enter directly into the alveolus. Thus, in order to maintain the integrity of the interstitium with respect to interstitial and lymphatic fluid drainage, which is compatible with life, the lining must be replaced. It is now known from studies in both animal and man that the Type II epithelial cell (also called the granular pneumocyte) is the cell type responsible for elaboration of surfactant (Fig. 15). It is also the reserve cell for repair of the alveolar epithelial integrity and lining.[3, 8, 14] It normally has a mitotic capability and, under the stimulus of interstitial injury, mitotic rate greatly increases and the cells rapidly proliferate in train-like fashion along the basement membrane. The ultrastructural morphology or normal Type II structure, as well as function and reparative capability, is depicted in Figure 15. In the scanning electron microscopic view, one can clearly see surfactant production with its actual secretion through the cell membrane into the alveolus. Also illustrated is light microscopic mitotic division of granular pneumocytes, and their proliferative "cuboidal cell" realignment of damaged alveoli so typical of the intermediate stage of repair in interstitial injury or pneumonitis. In the transmission electron micrograph, there are hyperplastic regenerating granular pneumocytes lining the basement membrane. One can visualize an increased number of phospholipid-containing lamellar bodies, which are the intracellular precursor of surfactant. In any given alveolus in the end-stage lung of ARI, one may find an admixture of normal surfactant-producing granular pneumocytes, degenerating granular pneumocytes, and hyperplastic granular pneumocytes, which appear to be secreting increased lamellar bodies. Thus, studies which attempt to quantify surfactant and to generalize on the primary or secondary role of surfactant production in ARI, utilizing bioassays on lavaged or homogenized segments of lung tissue, would seem to have little relevance to what is going on at the alveolar cell biologic level; the dynamics of surfactant production and destruction are rapidly undergoing change and vary from one alveolus to the next. Nonetheless, despite the complexity of this issue, there is no evidence whatsoever that primary surfactant deficiency resulting from granular pneumocytic injury is an identifiable problem. Clearly, any

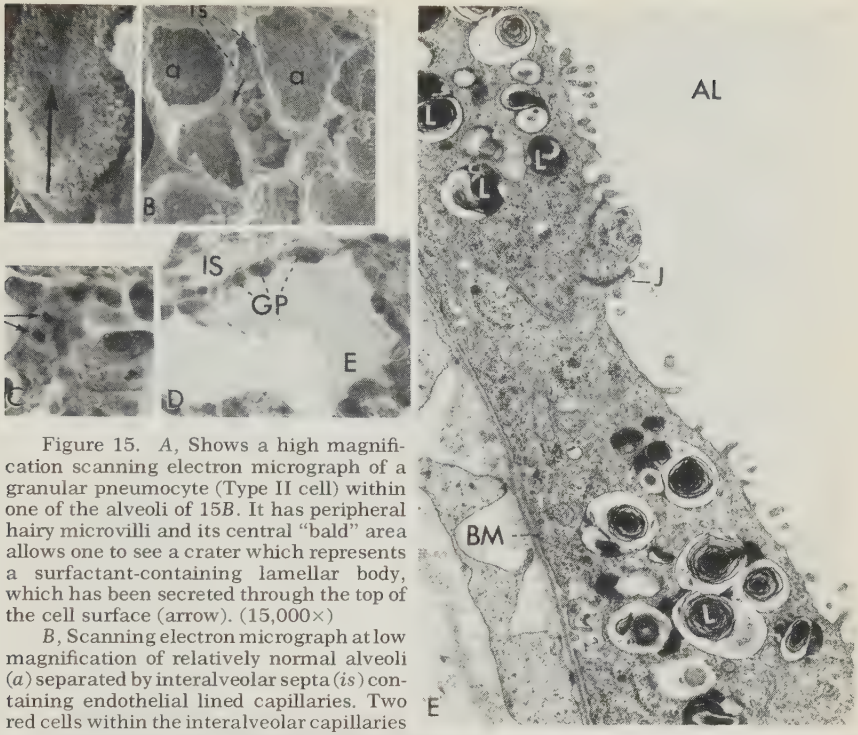

Figure 15. *A*, Shows a high magnification scanning electron micrograph of a granular pneumocyte (Type II cell) within one of the alveoli of 15*B*. It has peripheral hairy microvilli and its central "bald" area allows one to see a crater which represents a surfactant-containing lamellar body, which has been secreted through the top of the cell surface (arrow). (15,000×)

B, Scanning electron micrograph at low magnification of relatively normal alveoli (*a*) separated by interalveolar septa (*is*) containing endothelial lined capillaries. Two red cells within the interalveolar capillaries can barely be seen (small arrow). This tridimensional view gives an excellent understanding of the relationship of the pulmonary microcirculation and the intervening alveoli. It also indicates that one may find relatively normal foci of lung in end-stage ARI. (500×)

C, Lower left. Shows a metaphase mitosis (arrow), using light microscopy, in a region of granular pneumocytic (cuboidal lining cell) hyperplasia. (700×)

D, Lower right. Typical light microscopic histopathologic picture of so-called cuboidal lining cells (granular pneumocytic) hyperplasia. Intraalveolar edema (*E*) is also present. The cuboidal lining cells (*GP*) line the intraalveolar septum (*IS*). (480×)

E, Transmission electron micrograph of granular pneumocytic hyperplasia with one cell contiguous to the next (junction-*J*) aligning the basement membrane (*BM*). Alveolus (*AL*). Note the increase in phospholipid-surfactant-containing lamellar bodies (*L*). (16,000×)

demonstration of surfactant loss is due to the secondary effects of protein-laden edema fluid inactivation, which is a reversible factor more dependent on capillary leakage than on primary surfactant cellular production, since granular pneumocytic injury is an uncommon ultrastructural event in interstitial injury seen in ARI. Figure 16 shows a scanning electron micrographic tridimensional view of an alveclus where the normal epithelial lining is now completely replaced by cuboidal lining cells (granular pneumocytic hyperplasia). Since the thickness of granular pneumocytes is more than 10 to 15 times that of the normal alveolar lining thin Type I alveolar epithelial cells, and since physiologists calculate that the blood-air barrier must be thickened ten times before one gets diffusion

Figure 16. Scanning electron micrographic tridimensional view of an alveolus showing advanced granular pneumocytic hyperplasia characteristic of the middle and late stages of ARI. Numerous granular pneumocytes identified by their hairy microvilli cover the entire alveolar wall. A pseudopod of a pulmonary macrophage is stretched across the surface of the cell (MAC). A pore of Kohn is depicted with an arrowhead. The massive thickness of the cuboidal cellular lining of this alveolus would cause oxygen diffusion abnormality. (10,000×)

problems with oxygen transport (a so-called "diffusion block"), one can clearly appreciate, by tridimensional information of this type, that an alveolar diffusion defect is not only biologically possible, but indeed must occur in given alveoli (despite current physiologists' dogma that diffusion block doesn't exist). That is, the entire alveolus illustrated has its entire blood-air barrier covered by fat granular pneumocytes which impair the diffusion of oxygen. It is not our intent to in any way fight the accepted physiologic dogma of the 1970's that there is no such thing as a "diffusion block" and that all diffusion problems are really problems of altered ventilation perfusion inequality. As a physiologic teaching point for students, playing down the validity of "diffusion block" may be sound. But it is difficult for any physiologist to argue the point that in addition to obvious V/Q inequality within such lungs, alveoli such as the one illustrated herein have decreased diffusion through their blood-air membrane, particularly if cardiac output with resultant rapidity of pulmonary capillary blood flow is increased (as is so often the case in ARI). That is, the decreased pulmonary capillary red blood cell transit time will contribute to decreased red cell oxygenation in alveoli with thickened blood-air interfaces.

How Is the Injured Interstitium Which Is Lined by Nonphysiologic "Fat" Cuboidal Lining Cells (Granular Pneumocytes) Restored to Normal?

Recent studies on both humans and animals have indicated that the granular pneumocyte (Type II epithelial cell) which normally differen-

tiates to produce surfactant can undergo metaplasia and differentiate into a thin Type I alveolar lining epithelial cell.[3, 14] That is, after the regenerative alveolar granular pneumocytic process takes place, and the interstitial stimulus to cellular reactive hyperplasia is removed, the granular pneumocytes gradually become progressively thinner, lose their surfactant-producing organelles and gradually transform into perfectly normal Type I epithelial cells. This observation, in context of the lack of mitotic capability of the Type I cell, seriously raises the probability that all Type I cells may represent differentiation from the multipotential Type II granular pneumocyte. Figure 17 vividly demonstrates a number of Type II cells in various stages of metamorphosis or transformation back into Type I cells in ARI.

Capillary Endothelial Regeneration

Figure 17 shows evidence of capillary endothelial regeneration in the end-stage lung of ARI. The regenerating dark endothelial cells contain

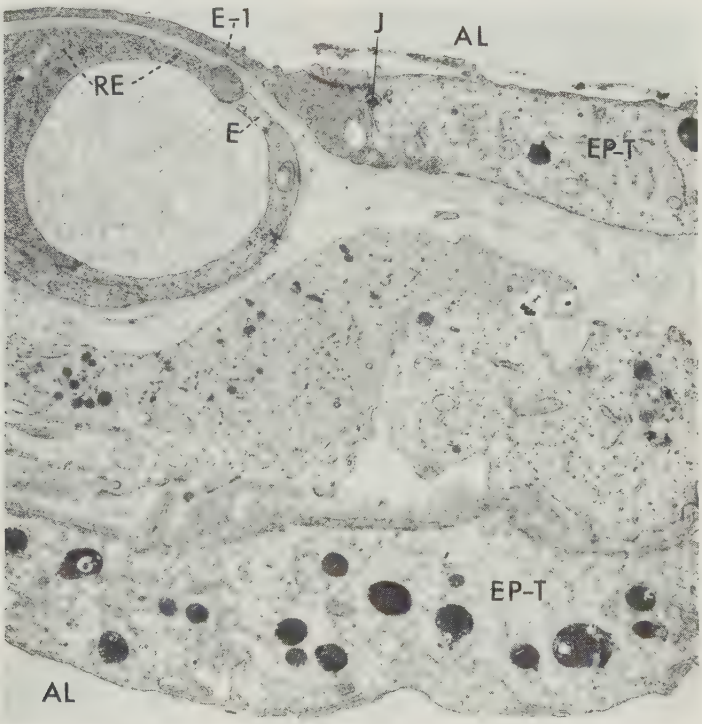

Figure 17. The alveolar epithelial lining cells show transition stage from Type II granular pneumocytes into progressively thinning Type I epithelial cells (*EP-T*). Alveoli (*AL*). Alveolar lining cells at the bottom show transformation from the concentrically whorled lamellar bodies into more neutral fat with decrease in width of the cell and loss of microvilli at the surface. The cell at the top contains even fewer degenerating lamellar bodies and is thinner, thus more approaching the morphology of a Type I cell lining cell. It makes a junction (*J*) with what appears to be a relatively normal Type I cell (*E-1*) showing decreased pinocytotic activity. The capillary at the upper left shows a regenerating endothelial cell (*RE*) with numerous dark free ribosomes, but no pinocytotic activity. It makes a junction with a hydropic, swollen degenerating endothelial cellular segment (*E*). (16,000×)

numerous free ribosomes which are responsible for protein synthesis for internal cytoplasmic repair. These cells are pushing away edematous and degenerating clear endothelial segments that have undergone irreversible injury. Such regenerating endothelial cells have few, if any, pinocytotic vesicles, consistent with the cell biologic principle that there is decreased enzymatic and functional differentiation during the process of regenerative repair. The documentation of such endothelial regeneration in injured pulmonary capillaries is encouraging since, if the patient can survive, or if he could be successfully tided over by extracorporeal membrane oxygenator support, the damaged capillary segments could be reconstituted as long as their basement membranes were intact. It has been of distinct interest that in these end-stage lungs evidence of endothelial regeneration has been more common than anticipated; and microthrombi, in relation to the endothelial damage present, have been surprisingly rare.

Bacterial Defenses in Relation to Complicating Fatal Pneumonia

The last composite of illustrations depicts virtually the entire sequence of cell-biologic ultrastructural phenomena in relation to bacterial defense and the morphogenesis of bacterial pneumonia complicating ARI. Pseudomonas has been perhaps the worst offender in patients dying in intensive care units. Despite good reviews on general defense mechanisms of the lung,[20, 26] we still know very little about the pathology of altered host defenses in patients with ARI. We do not know whether they differ in any way from those seen in any debilitated patient who has antecedent lung disease and pulmonary edema (which in and of itself represents very fertile soil for bacterial replication and secondary infection).

Figure 18*A* illustrates the mucociliary clearance of Pseudomonas by tracheobronchial cilia. Many subtle or noxious stimuli alter the rhythmicity of ciliary movement and little is known about the biochemical alterations occurring in mucus secretion in patients with ARI who are treated with ventilatory support and high concentrations of oxygen. The latter is known to interfere with ciliary function. If the illustrated mucociliary clearance apparatus fails in its attempt to eliminate colonization of the tracheobronchial bacteria, the pulmonary macrophage depicted in Figure 18*B* must now rid the same Pseudomonas bacillus from the alveolus (Fig. 18, *A*, *B*, and *D*). There is a growing list of variables which are now known to decrease the bacteriocidal capability of these phagocytes, including ethanol, toxic concentrations of oxygen, and inhalation of certain noxious fumes. With respect to the latter, cigarette smoking constitutes the most ubiquitous cause of mucociliary dysfunction, and thus, smokers with bronchitis are more prone to complicating fatal bronchopneumonia. Figure 18*C* shows a Pseudomonas bacillus in the process of division within the lung's interstitium. Pseudomonas aeruginosa produces a severe necrotizing bronchopneumonia which is highly resistant to antibiotic therapy. In part, its capability to induce necrotizing reactions is due to the host of exotoxins which it produces (Pseudomonas is peculiarly deficient in endotoxin as compared to other Gram-negative bacilli). The ultrastructural evidence for the specific production of collagenase by this bacillus can be seen by the dissolution of collagen bundles contiguous to the

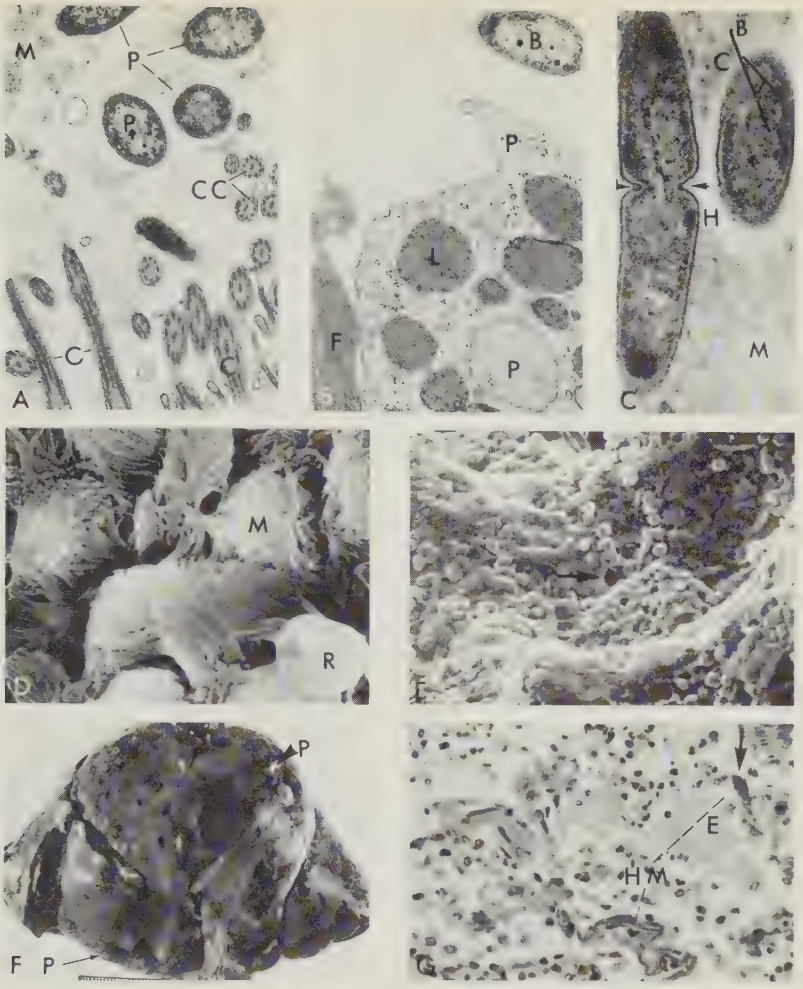

Figure 18. Defense mechanisms. *A*, Bronchial cilia are seen standing on edge (*C*) and in cross-section (*CC*) beating up gray mucus (*M*) containing Pseudomonas aeruginosa (*P*). (15,000×)

B, A pulmonary macrophage crawling on fibrin (*F*) containing lysosomes (*L*) and phagosomes (*P*) sends a pseudopod (*P*) after an intraalveolar Pseudomonas bacillus (*B*). (16,000×)

C, Shows a high magnification view of Pseudomonas aeruginosa undergoing division (at arrow head). The bacillus (*B*) which produces a necrotizing bronchopneumonia in patients with ARI, has invaded the pulmonary interstitium. Collagenase produced by the organism is evidenced by the halo (*H*) which represents dissolved collagen (*C*) and mucopolysaccharide ground substance (*M*). (10,000×)

D, Shows a tridimensional view of the tracheobronchial cilia which look normal in this micrograph. There are interspersed mucus-producing cells (*M*) and an apple-shaped red cell (*R*) is present at the bottom right. (5,000×)

E, Shows a tridimensional view of terminal bronchopneumonia in ARI with alveolar sacs and their contiguous alveoli containing numerous degenerating leukocytes in this scanning electron micrograph. A pore of Kohn (*P*) is demonstrated by the arrow.

F, The gross picture of end-stage ARI with pneumonia. Dark areas of hemorrhagic Pseudomonas pneumonia (*P*) complicating the already bulging and consolidated lung typical of end-stage ARI.

G, Shows the light microscopic picture of typical bacterial bronchopneumonia with neutrophils filling alveolar spaces also containing edema fluid (*E*) and fragments of hyaline membrane (*HM*). There is early interstitial fibroblastic ingrowth into the hyaline membranes (arrow). (300×)

invading bacilli (Fig. 18*C*). Finally, the all too familiar and sad light microscopical picture of bronchopneumonia amidst a residuum of hyaline membranes within the lung of ARI is depicted in Figure 15*G*. A scanning electron micrograph (Fig. 15*E*) taken from the same field shows the bodies of neutrophils resting on the alveolar walls within an alveolar sac, rendering the macabre impression of a World War I battle scene on the hills of alveolar sacs. Figure 15*F* grossly demonstrates fatal Pseudomonas pneumonia complicating the already consolidated lung of ARI. The successful treatment of appreciable bacterial pneumonia complicating acute respiratory insufficiency has remained, and probably will remain, an almost insurmountable problem with regard to both prevention and treatment. The underlying pathology of ARI is so devastating that both patient and physician have little in the way of beneficial natural resources to successfully deal with the problem.

SUMMARY

The straightforward core pathobiologic facts needed for the clinician's basic understanding of the clinical course and pathophysiology of progressive acute respiratory insufficiency (ARI) seen in surgical practice are summarized in the opening paragraphs. The remainder of the article provides the detailed evidence for elucidating the morphogenesis, i.e., the sequence of pathologic events, which determines the natural and the therapeutically altered clinicopathophysiologic courses of ARI. The attempt is to integrate observations concerning altered structure, cell biology, pathophysiology, physiologic function test data, bioengineering principles, clinical course, therapeutic management, and historical aspects of the disease process, into a detailed multidisciplinary but comprehensive explanation of this very complex, difficult disease process.

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Endocrine Control of Plasma Protein and Volume

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The control of blood volume depends not only upon the control of intake and output of water and electrolyte, but also upon the movement of fluid among the vascular, interstitial, and intracellular compartments. Such shifts are rapid, and form the first line of defense against rapid losses of volume that occur, for example, with hemorrhage and trauma. The content of protein, principally albumin, is of prime importance in determining the distribution of fluid among body compartments. Recent evidence suggests that multiple endocrine functions, but particularly those of the adrenal glands, play a central role in the control of plasma volume and protein, and thus in the homeostatic regulation of blood volume.

The Requirement for Restoration of Blood Volume After Hemorrhage

The loss of blood volume results in a rapid response of the sympathetic nervous system mediated through the classical baroreceptor reflex. There is an increase in heart rate and total peripheral resistance associated with arterial vasoconstriction, and there is shunting of blood flow through some organs. In this way, the restricted cardiac output is redirected to maintain perfusion pressure and flow to vital organs such as the brain and heart. However, if the sympathetic response persists, tissue hypoxia, shock, and even death may ensue. In part, this is believed to be the result of acidosis associated with the tissue hypoxia and the resultant hyperkalemia. Recent evidence suggests that small molecules such as kinins and prostaglandins may also be involved in the mediation of the deleterious results of the sympathetic vasoconstriction. In order to turn off the sympathetic response, it is necessary to increase the stimulation of baroreceptors and of other cardiovascular receptors. The only physiologic mechanism available to do this is restitution of the blood volume itself. Thus, the restoration of blood volume is a fundamental requirement for survival after hemorrhage.

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The Restitution of Blood Volume

The restitution of blood volume occurs in two principal phases. The first phase is mediated by the sympathetic response to blood loss itself and is responsible for approximately 20 to 50 per cent of blood volume restitution, depending upon the magnitude of hemorrhage. This phase is initiated by the fall in capillary pressure that follows arteriolar vasoconstriction, as well as by the direct fall in arterial pressure resulting from the loss of blood.[9, 26] As capillary pressure falls, protein-free fluid moves from the interstitium to the capillaries, thus restoring blood volume. However, as this fluid moves, interstitial pressure falls and capillary oncotic pressure also falls. As a result, a pseudoequilibrium is reached, that may begin as early as 30 minutes and last as long as 6 hours, as the changes in interstitial hydrostatic and capillary oncotic pressure offset the initial fall in capillary hydrostatic pressure.

A second phase of blood volume restitution then follows in the normal state and depends upon the simultaneous restitution of plasma protein, primarily albumin.[11, 41] A number of workers have demonstrated that the albumin delivered to the circulation during this phase must be preformed rather than newly synthesized, since the synthesis of new albumin does not begin for approximately 2 days after hemorrhage.[2, 30] It has also been suggested that the increase in plasma protein may be brought about by limiting the extravasation of protein from the capillaries rather than by delivering excess protein to the blood.[48] However, quantitative consideration of the amount of protein which could be accumulated as a result of limited loss, that might result in turn from vasoconstriction, shows that only about 30 per cent of the lost protein can be regained by this mechanism.[35] Since the capillaries are impermeable to protein, the movement of protein into the circulation must be through the lymphatics. The driving force for lymphatic return is primarily the pressure within the interstitium.[25] As noted above, interstitial pressure falls following hemorrhage as a result of the first phase of restitution of blood volume, thus limiting lymphatic flow. Since tissue compliance is believed to be more or less fixed, an increase in pressure within the interstitium implies an increase in interstitial volume.[25] Thus, if there is to be a suitable driving force for lymphatic return after hemorrhage to initiate the second phase of volume restitution, interstitial volume must increase. In the absence of exogenous input to the interstitial volume, there must be a shift of fluid from the cells to the interstitium in order to increase that volume.[35]

Fluid Shifts

The shift of fluid from cells to the interstitium implies an osmotic gradient between intracellular and extracellular compartments, with increased osmolality on the outside. Boyd and Mansberger[5] first called attention to the increase in plasma osmolality occurring in severely injured patients as well as in experimental animals. Increases in plasma osmolality also follow even minor stresses in the rat,[16] and occur promptly after even small hemorrhage in the dog.[20] The increase in osmolality not

only occurs promptly, but appears to be sustained for a period of hours or days. Both the magnitude and duration of the osmotic increase appear directly related to the degree of volume loss or of injury. The constituents of solute responsible for the increase in osmolality have been examined by Boyd and Mansberger and by ourselves.[37] On the basis of preliminary investigations, it may be concluded that sodium, potassium, glucose, and urea are not responsible for any of the increase in osmolality following small hemorrhage. The contribution of urea and of glucose increases as the magnitude of volume loss increases, so that in severe hemorrhage in man there may be severe hyperglycemia, as shown by Carey and his associates.[6] The increase in urea probably reflects increased gluconeogenesis, and preliminary experiments suggest that there may be some increase in circulating amino acids as early as 2 or 3 hours after hemorrhage. It has also been noted that the osmotic constituents vary at different times following volume loss. The degree of fluid shift which may follow hemorrhage, presumably mediated by this increase in osmolality, has been a matter of considerable disagreement. Stewart and Rourke[42] first measured a shift of fluid from cells to interstitium in 1936. Subsequent workers have either confirmed[43] or failed to confirm[14, 31] their observations. However, most situations in which workers were unable to observe such shifts have been associated either with severe shock[14] or with a stress situation preceding the observations of fluid volume.[31] In recent experiments in our laboratory, we have been able to prevent the fluid shift by prior adrenalectomy, as described below.[20, 37] As a result, we could investigate the effect on the return of plasma protein and volume after hemorrhage resulting from exogenous infusion of fluid in the absence of a shift from cells to interstitium.[37] As predicted, infusion of colloid-free fluid can induce significant, and in fact complete, restitution of plasma protein and volume in the absence of such a shift. However, in the absence of the infusion of the exogenous fluids, the evidence supports the hypothesis that such fluid shifts are essential and are dependent upon increases in plasma osmolality.

Hormonal Induction of Increased Extracellular Osmolality

Experiments in our laboratory have demonstrated that an increase in plasma concentration of cortisol is required to induce an increase in extracellular osmolality following hemorrhage.[37] In experiments in adrenalectomized dogs, we have shown that a constant infusion of cortisol sufficient to maintain basal concentrations in plasma did not permit expression of hyperosmolality after hemorrhage. In contrast, infusion of cortisol at a physiologically increased rate, so that plasma levels mimicked those seen after hemorrhage in intact animals, allowed full expression of hyperosmolality for the first 90 minutes following hemorrhage. However, after this time, adrenalectomized animals replaced with cortisol alone returned their osmolalities to normal, whereas intact animals maintained the hyperosmolality for an additional 4 hours. This suggests that an adrenal factor, in addition to cortisol, is necessary for full expression of the hyperosmolality following hemorrhage, and thus implies that cortisol is not sufficient to initiate and support this response. The

administration of large doses of desoxycorticosterone did not change the hyperosmotic response. In addition, as has been pointed out previously, renal conservation of sodium and water can limit losses following hemorrhage and are thus essential to the metabolic response to blood loss, but cannot contribute directly to the restitution of blood volume in the absence of increased fluid intake.[26] That cortisol is not a sufficient factor for the induction of hyperosmolality after hemorrhage is also clear from the fact that infusion of cortisol at physiologically increased rates in the absence of hemorrhage led to no changes in extracellular osmolality.[37] However, the action of cortisol is not permissive, as has been suggested in the past by Ingle and his associates,[28] since the infusion of cortisol at basal rates was not sufficient to allow expression of hyperosmolality. These findings imply that cortisol and an additional adrenal factor, and at least one other factor initiated by hemorrhage, must cooperate in the full expression of the hyperosmotic response.

In a search for an additional factor, dogs were studied following hypophysectomy and maintenance with cortisol. Following a 10 per cent hemorrhage and physiologic increase of the rate of infusion of cortisol, these animals showed no change in plasma osmolality. At 24 hours, there was a 30 to 40 per cent return of plasma protein as well as of plasma volume. This degree of protein restitution would be equivalent to that seen were the limitation of protein loss effected by vasoconstriction to be operative, as suggested by Zollinger. These results implied that one or more pituitary factors also must be involved in the hyperosmotic response to loss of blood volume.[36] It has been shown previously that secretions of prolactin,[24] growth hormone,[33] and ACTH[19] from the anterior pituitary and vasopressin[47] from the posterior pituitary are all increased following hemorrhage. In addition, hemorrhage, by activating the sympathetic response, also leads to increases in the secretion of glucagon and renin, which in turn leads to increased plasma levels of angiotensin II. It is possible that several or all of these factors are involved in the cooperative mediation of increased extracellular osmolality following hemorrhage. In fact, it is tempting to speculate that the early neuroendocrine response to the loss of volume and to trauma is organized for the appropriate increase of extracellular osmolality through early features of the metabolic response to injury. In this sense, the hormonal induction of extracellular hyperosmolality may be viewed as the first step in the metabolic response to injury. Furthermore, the late and ultimately deleterious effects of the metabolic response may prove to be simply a sort of metabolic payoff for this early and homeostatically oriented response.

Neural Control of Hormonal Secretion

The possibility of a multihormonal coordinated response to hemorrhage, organized for the restitution of blood volume suggests in turn a common mechanism for the control of release of these hormones in response to loss of volume. The details of the central neural mechanisms controlling hormonal secretion in response to hemodynamic changes are poorly understood. However, a number of these details have been worked out recently, at least for the control of release of ACTH. It appears clear

that both atrial and carotid vascular receptors are involved in the control of secretion of ACTH.[12, 17] Furthermore, early in hemorrhage, when volume loss is low, the role of the atrial receptors, particularly those in the right atrium, appears to be dominant.[3, 13] Both atrial and carotid receptors have been shown to project through the Xth and IXth cranial nerves, respectively, to the region of the solitary nuclei in the medulla. Recent studies in our laboratory have identified three distinct areas in this region receiving afferent input from atrial receptors, and activated or inhibited by stretch of the right atrium.[4, 45] In the case of a number of cells studied, carotid sinus nerve stimulation also changed the neural activity of the cells in directions similar to those induced by atrial stretch. A number of these cells have been shown to project without synapsing to the dorsal rostral pons, particularly in the region of the locus subceruleus but also to the principal locus ceruleus and lateral ventral tegmental nucleus.[45] From this point, it appears that the cells project, again without synapsing, to the medial dorsal hypothalamus.[8, 23] An additional ventral pathway has also been identified which traverses the interpeduncular nucleus, the mamillary bodies, and the median forebrain bundle to end in or near the suprachiasmatic nucleus of the hypothalamus. In the case of this latter pathway, the number of synapses appears to be greater, but in either case the pathway must be described as oligosynaptic, since the number of neurons needed to traverse the functional path from atrium to hypothalamus may range between three and seven. Electrical stimulation of the pertinent synaptic regions defined above has shown that each of these regions is involved in the control of ACTH, and that stimulation of specific nuclei within each region may lead to facilitation or inhibition of release of ACTH.[22, 23, 46] Furthermore, the nuclei involved are also related to the control of sympathetic outflow, as evidenced by changes in arterial resistance and in renal vascular resistance.[1] Thus, the same nuclei may be involved in the control of secretion of glucagon, insulin, and renin. It is interesting that in our search for central projections of vascular afferents, we have found no central projections stimulation of which did not change release of ACTH. This finding suggests that the brainstem pathways mediating release of ACTH are shared in the control of other hormones as well. To some extent, this suggestion has been confirmed for vasopressin.[37] Thus, it appears that the central neural components underlying the neural control of hormonal secretion are organized to support a coordinated and multihormonal response to the loss of blood volume.

The Detection of Blood Volume

As indicated above, the primary receptors that sense a reduction in blood volume lie in the right atrium. When artificial hemodynamic stimuli are introduced experimentally to play one receptor group against another, stimulation of the right atrial receptors can prevent a hormonal response to less stimulation of another receptor group.[3] Conversely, a reduction in activity of right atrial receptors will lead to a release of ACTH even when the activities of other receptors are increased. Like other stretch receptors, the right atrial receptors are sensitive both to the degree and to the rate of change of stretch. They normally fire during the atrial v-wave,

which occurs during the period in the cardiac cycle when the atrioventricular valve is closed. Accordingly, the slope of the v-wave is proportional to the rate of inflow of blood into the right atrium, that is, to the venous return. It is, furthermore, this slope which drives the rate-sensitive element of the receptor. The proportional-sensitive element of the receptor is in turn proportional to the actual amount of atrial filling, that is, to the total extent of venous return at a given time. Thus, these receptors are in a peculiar position to sense both the rate and the amount of venous return, and thus, of cardiac output.[21] For some years, workers have spoken of "effective blood volume" as a key factor in the control of salt and water retention and of hormonal responses to changes in blood volume. With the identification of the atrial receptors as pivotal, it now appears that the effective blood volume can be viewed as venous return itself. Because of the properties of the atrial receptors, the hormonal responses to loss of blood volume can be sensitive not only to the total amount of loss but also to the rate of loss. That this is the case has been demonstrated thus far for ACTH and cortisol,[18] for vasopressin,[10] for renin,[10, 27] and for catecholamines.[7] Furthermore, the integration of the neural mechanisms described above allows the system controlling hormonal secretion to integrate impulses from arterial as well as from atrial receptors and, thus, to derive a measure of the total amount of volume lost. For a number of hormones, including ACTH and cortisol,[18] vasopressin, and renin,[10] the hormonal secretion rates are exquisitely tuned to reflect the degree of volume loss.

Thus, it appears that in response to hemorrhage, as shown in Figure 1, the loss of volume and the rate of loss of volume are sensed by cardiovascular system receptors that normally exert tonic inhibition, through the central nervous system, on the secretion of a variety of endocrine glands and on the activity of the sympathetic nervous system. With the release of this inhibition, integrated through central neural mechanisms shared by the sympathetic nervous system and by a number of endocrine functions, there is increased sympathetic activity and increased release of a battery of hormones. The changes in sympathetic function and in endocrine function act in concert to promote compensatory changes in the vascular system reflected in changes in resistance, heart

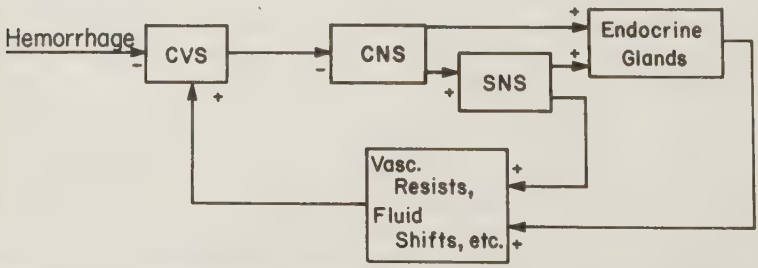

Figure 1. The neuroendocrine response to hemorrhage, viewed as a closed-loop negative feedback control system organized for the regulation of blood volume. Abbreviations: CVS, cardiovascular system (and associated receptors); CNS, central nervous system; SNS, sympathetic nervous system; +, stimulation; −, inhibition.

rate and contractility, and also to promote a series of shifts of fluid, first directly from the interstitium and later from cells to interstitium to blood, which leads also to the mobilization of protein transfer from the interstitial to the intravascular compartment. It is this set of fluid shifts and the concomitant restitution of plasma protein that ultimately effects the restitution of plasma volume and protein and that ultimately leads to the termination of neuroendocrine response to hemorrhage. According to this concept, the neuroendocrine response to hemorrhage can thus be viewed as a negative feedback control system organized for the control of blood volume.

CLINICAL IMPLICATIONS

The loss of blood and commonly associated trauma lead to a pattern of changes in whole body metabolism commonly referred to as the metabolic response to injury.[34] In studies of this process, attention usually has been focused on relatively late effects, most of which are detrimental to the welfare of the patient. Included among these are prominent protein wasting associated with gluconeogenesis and with increased mobilization and utilization of fatty acids, and a prolonged intolerance to and decreased utilization of glucose. Although there is considerable controversy concerning the relative roles of various hormones secreted in response to volume loss and to injury, there is general agreement that the metabolic response to injury is a direct consequence of the neuroendocrine response to injury. In light of what has been said above, it seems reasonable to view the classical metabolic response to injury as a late and detrimental result of an early and functionally critical response to volume loss, organized primarily to restore that loss. The vascular receptors that initiate the neuroendocrine response can be stimulated by volume replacement, and it has been shown that such stimulation can decrease and even eliminate the hormonal response. Accordingly, prompt complete replacement of volume is the treatment of choice if the late consequences of the neuroendocrine response are to be averted. Indeed, with respect to a number of hormones, it has been shown that expansion of the blood volume or increase in blood pressure can prevent hormonal responses to stimuli other than volume loss.

The definition of a small number of central neural pathways mediating a concert of endocrine responses, and the participation in these pathways of a limited number of neurotransmitters suggests the possibility that ultimately it will be possible to block significant features of the neuroendocrine response to injury by the use of pharmacologic agents which will act centrally. However, at the present time this hope has not been realized and must await further delineation of the system.

The rise in plasma osmolality that follows injury and hemorrhage is roughly proportional both in extent and duration to the magnitude of the volume loss.[5, 6] Accordingly, the degree of rise in plasma osmolality can be used to infer the degree of severity of the insult that the patient has suffered. Both plasma osmolality and plasma glucose have been used in

this respect to separate potential survivors from those who will not survive. Because of the osmotic gap identified by Boyd and Mansberger and confirmed, subsequently, in our own laboratory, measurement of osmolality seems to be a better index of severity than does measurement of glucose alone.

In the presence of severe hypotension, adrenal blood flow is limited, so that increased cortisol secretion will not follow increased plasma levels of ACTH.[29] In the presence of slow bleeding, however, plasma levels of cortisol will increase prior to the severe hypotension and will be maintained by the concomitantly decreased hepatic blood flow. However, if the onset of shock is rapid, there may be shock without increased corticosteroids. This situation apparently obtains in experimental animals. The presence of such a syndrome in man has not yet been identified, however. Similarly, experiments in rats have shown that after an extreme stress, there may be a late period of pituitary insufficiency, so that ACTH can not be released in normal amounts from the pituitary, even when the pituitary is stimulated by corticotropin releasing factor.[15] Should either of these situations exist in man, there may be a group of patients who present with relative adrenal insufficiency. If the role of the adrenal cortical mechanism outlined above is essential for blood volume restitution in man, as it is in the dog, volume restitution will be impaired in such patients. This situation may provide an indication for physiologic replacement with corticosteroids. At the present time, however, there is no indication that increased concentrations of corticosteroids beyond the physiologic will be of further benefit to restitution of blood volume.

As described above, the administration of noncolloid electrolyte solutions, especially if they are given rapidly, can lead to significant increases in extracellular fluid volume and pressure and, thus, lead to movement both of fluid and of protein into the plasma. Because of the movement of protein, there will be a disproportionately large retention of infused fluid in the plasma compartment at equilibrium. As a result, the administration of blood can be avoided in the presence of moderate hemorrhage by the administration of adequate quantities of electrolyte solution. The ultimate limiting constraint is a reduction in hematocrit to unsafe levels. It is possible to calculate that blood loss of the order of 75 per cent of the blood volume could be replaced in this manner without reducing the hematocrit below 10. However, Rush and Eiseman apparently found a limit of 66 per cent hemorrhage with one protocol in dogs under pentobarbital anesthesia.[38] Of greater clinical importance, however, is the suggestion that the addition of electrolyte solution may render the replacement of blood loss more effective by increasing interstitial pressure. Such administration will not only lead to the addition of protein and fluid to the circulation to increase the expansion of blood volume per se, but will also reduce the leakage of blood into the interstitium. Thus, the mechanism outlined above appears to support evidence that the administration of colloids should be accompanied by the administration of noncolloid electrolyte.[39]

Shires and his associates[40] have advanced evidence for loss of membrane stability in shock with attendant reduction in the efficacy of the

sodium pump. Such instability of cell membranes implies changes in cellular metabolism that may in turn have direct detrimental consequences. In addition, however, it is clear that if the sodium pump is not effective, then increases in nonelectrolyte osmotic constituents in the interstitium cannot draw significant quantities of fluid from the cells to the interstitium since the retained intracellular sodium will act as a force in the opposite direction. In this situation, the physiologic mechanism to support restitution of blood volume, and thus, of cardiovascular function, cannot be effective. Accordingly, in the state of profound shock, the loss of a mechanism to shift fluid from the cells to the interstitium, and thus to support the restitution of plasma volume and protein, can contribute to the vicious spiral leading ultimately to irreversibility.

SUMMARY

The loss of blood volume initiates a sequence of events that begin with detection of the volume loss by cardiovascular receptors and the transmission of the signals of that loss to the central nervous system. Central neural processing leads to the release of multiple hormones that act together to induce an increase in extracellular osmolality. In response to the increase in extracellular osmolality, fluid shifts from cells to the interstitium, increasing interstitial volume and pressure. The increase in interstitial pressure leads to increased capillary and lymphatic return of fluid and to increased lymphatic return of preformed albumin. These events combine to form the second definitive phase of the restitution of blood volume, which is crucial both for the support of critical cardiovascular function and for the inhibition of the initial neuroendocrine response. If left unabated, this response may lead to the detrimental features of the metabolic response to injury. The degree of hyperosmolality following volume loss in injury may serve as an index of severity of that injury. The presence of the mechanism outlined provides a further rationale arguing in favor of prompt and adequate fluid therapy of the injured and volume-depleted patient.

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Multiple Systems Organ Failure: Muscle Fuel Deficit with Visceral Protein Malnutrition

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The patient with trauma who develops sepsis with multiple systems organ failure is highly likely to die. An improved understanding of this state is of the greatest importance since it seems to be commonly associated with death in the intensively supported patient where death from the initial shock state and later cardiopulmonary failure are prevented. Clearly there is ample time for therapy if we only know what therapy to provide. One aspect of this problem related to protein malnutrition will be discussed in this paper.

During the past 10 years we have studied in one way or another all patients admitted to the trauma service at the E. J. Meyer Memorial Hospital with life-threatening injuries. This service in a typical year admits 1000 patients, operates on 600 patients, and has 90 to 100 patients in the Intensive Care Unit. Two hundred and six of these patients were reviewed, with 53 being reviewed in detail. Fourteen out of the 53 patients died. These 53 patients had 161 separate injuries (three apiece). The behavior of the 53 reflected accurately the behavior of the 206 with respect to the sequence of organ failures.

CLINICAL BACKGROUND

The data reveal that, apart from the initial shock, multiple systems organ failure is a cumulative sequence of organ failures in which pulmo-

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nary failure occurs first, right ventricle failure second, and various hepatic dysfunctions, the most obvious of which are those of jaundice and hypoalbuminemia, occur third. These occur typically at 7 to 14 days. These hepatic dysfunctions must be distinguished from those that occur on the second to fourth day which are clearly related to the initial shock and seem to have no more prognostic value than the shock indices have. If the pulmonary failure can be reversed, the hepatic dysfunctions reverse and the patient recovers. If the pulmonary failure cannot be reversed then the hepatic dysfunctions persist even though the measured cardiac outputs are considerably above normal and arterial oxygen tensions of 100 can be maintained with ventilatory support. These observations are almost always associated with fever, and leukocytosis and sepsis. However, it should be noted that there is a significant fraction of such patients (about 1/3) in whom no area of sepsis or bacteremia is ever identified. If the hepatic dysfunctions persist, with additional time there is increasing probability of the following associated organ failures: (1) late gastrointestinal stress ulceration (clearly different from that immediately post shock); (2) sepsis with normally noninvasive organisms; (3) decubital ulcers; (4) wounds that do not heal; (5) lack of formation of granulation tissue in areas of sepsis and in open wounds; (6) the requirement for increasing quantities of albumin to maintain the plasma albumin; (7) the lethargic to comatose state; and (8) reduced cellular and humoral immunity.

These observations are associated in the absence of exogenous albumin support with hypoalbuminemic edematous oliguria characterized by a higher than normal central venous pressure, hyponatremia, hypochloridemia, a slight metabolic acidosis, respiratory alkalosis, and a distinct tendency towards hypotension and oliguric renal failure. These characteristics of this state may be largely reversed with the use of exogenous albumin to maintain the plasma albumin. However, the measured blood volume required to maintain adequate circulation slowly increases with time and minor degrees of hypovolemia which would not normally be associated with hypotension may now be associated with hypotension. When the volume needs are carefully met and plasma albumin maintained, then by examination one finds, in association with the jaundice and hypoalbuminemia, that the liver has enlarged and some degree of ascites is present even though peripheral edema has been largely avoided. The enlarging liver best correlates with the amount of glucose being given relative to the amount of nitrogen as amino acids. The enlarged liver may be reduced in size by increasing the amino acids and reducing the amount of glucose.

Terminally these patients develop a deficiency of most clotting factors including the thrombocytes in association with severe biventricular failure and die with massive bleeding and a circulation that is largely unresponsive to volume and to positive inotropic agents.

Clearly the best way to avoid these catastrophes is to avoid sepsis. However, it seems highly unlikely we will ever completely accomplish this in severely injured man. Further, as will be discussed subsequently, it would appear there are avenues of therapy which are completely un-

explored which should have the potential for metabolically increasing antibacterial resistance at about the tenth to fourteenth day where we have the most trouble.

BIOCHEMICAL BACKGROUND

The manifestations of multiple systems organ failure undoubtedly have a very complicated pathophysiologic background. However, all may be interpreted to reflect a limited protein synthesis. Protein synthesis requires a balanced mixture of amino acids, the protein synthetic apparatus, and a source of calories as ATP. The protein synthesis occurring in the viscera (liver, gastrointestinal tract, and pancreas) appears to be under fundamentally different controls from the protein synthesis in the systemic body.[16] Protein synthesis in the viscera is increased after every meal and seems to be largely controlled by the rate at which a balanced mixture of amino acids plus calories are supplied. In contrast, protein synthesis in the systemic body is largely related in one way or another to the work required of an organ and largely independent of the rate at which amino acids are supplied.

Most of the body can derive calories as ATP either from glucose or free fatty acids. The oxidation of free fatty acids in general requires the presence of a quarternary ammonium compound called carnitine as a transport agent from the cytoplasma into the mitochondria.[11] Glucose and ketone bodies are in general oxidized independently of carnitine. Carnitine is synthesized in the liver from various precursors including methionine and lysine. Certain organs have very specific requirements for caloric sources while other organs may burn almost any substrate for energy. Thus the heart and respiratory muscle may burn almost any substrate while the brain has a specific requirement for glucose under normal conditions. Under conditions of prolonged starvation the brain may also burn ketone bodies for a significant portion of its energy.[20] Ketone bodies in many ways must be considered as a water-soluble, carnitine, independent energy source equivalent to glucose but derived from fat.[18]

Striated skeletal muscle apart from respiratory muscle also appears to have specific energy requirements in that it has a very limited ability to oxidize glucose and a strong requirement for long chain fatty acids or ketone bodies.[1] Muscle, however, has the additional adaptation in that it may oxidize the essential branched chain amino acids as a source of energy.[12, 17] Muscle may also oxidize or at least interconvert a variety of other amino acids under specific circumstances with the specific exceptions of tryptophan, proline, arginine, and ornithine.[12] The amino acids constitute another carnitine independent energy source for muscle similar to the ketone bodies. Leucine and isoleucine are probably converted in the muscle to ketone bodies before being oxidized. The nitrogen derived from oxidation of the branched chain amino acids in muscle and probably several others may be released and transported back to the viscera as alanine.[9] Ammonia released in muscle or derived from the plasma plus

other amino acids may be released and transported to the viscera or kidney as glutanine.[12] Muscle may utilize glucose in the glycolytic cycle with the release of lactate and production of ATP.

The net amino acid effects of muscle amino acid metabolism is that it creates an amino acid mixture rich in alanine and glutamine.[21] A normal activity of the liver is to clear and catabolize all amino acids present in excess of a balanced amino acid mixture with the specific exception of the branched chain amino acids which are largely catabolized in the muscle to alanine and glutamine.[8] Thus the muscle activity converts these excess branched chain amino acids to ones the liver can utilize for gluconeogenesis, and since they are now in excess relative to the other amino acids, the muscle activity largely controls in the absence of oral intake hepatic amino acid gluconeogenesis. In the presence of oral intake all amino acids in excess of hepatic protein synthetic capacity may be utilized for gluconeogenesis either directly or for the branched chain amino acids indirectly via muscle.[8]

Muscle normally obtains the bulk of its energy from long chain fatty acids or ketone bodies and consumes branched chain amino acids only to the extent they are in excess of protein synthetic requirements in the viscera.[1] The long chain fatty acids may be obtained from the plasma free fatty acids or the plasma triglycerides. The plasma glucose normally has a reciprocal relationship to the plasma free fatty acids and ketone bodies and a direct relationship to the plasma insulin.[4] The plasma insulin can activate lipoprotein lipase and thus free long chain fatty acids from the triglycerides. It appears highly probable in the postprandial state and certain hyperglycemic states that are associated with low plasma free fatty acids and ketone bodies that a dominant source of energetic substrate for muscle are the plasma triglycerides. These are also the circumstances in which hepatic synthesis of the lipoproteins and their contained triglycerides are apt to be maximal.[4] The increased production of triglycerides and lipoproteins with increased muscle oxidation of long chain fatty acids derived from plasma triglycerides is probably an essential part of successful adaptation to intravenous hyperalimentation. In contrast in the normal fasting state a dominant source of muscle energetic substrate will be the plasma free fatty acids and ketone bodies. The exact proportion of these two energetic substrates will depend upon the muscle carnitine available to transport the long chain fatty acids into the mitochondria. Clearly with increasing time of starvation, the muscle burns less and less ketone bodies and more long chain fatty acids.[19] Associated in time with this is an increase in the muscle carnitine.[6] Presumably the two are related.

HYPOTHESIS

Sepsis is well known to be associated with hyperglycemia, increased insulin, reduced plasma free fatty acids, and reduced ketone bodies.

There are some observations which suggest that it is associated with increased triglycerides. If no carnitine limitation of long chain fatty acid oxidation occurs and if the triglycerides and insulin are elevated and if the insulin can activate the lipoprotein lipase, muscle could obtain its energy in the face of low free fatty acids and ketone bodies from the long chain fatty acids in triglycerides. However, if the triglycerides are not elevated or the lipoprotein lipase not activated, a muscle fuel deficit will occur.

There are observations which show a reduced muscle carnitine with sepsis in the dog and man.[6] Comparable decreases in myocardial carnitine have been shown to restrict long chain fatty acid oxidation in experimental diptheritic myocarditis and not to restrict the oxidation of carnitine independent energetic substrate.[22] If a muscle carnitine deficiency occurs which limits long chain fatty acid oxidation, energy from either the plasma long chain fatty acids or triglycerides cannot be obtained. If this also occurs in the presence of an inadequate hepatic output of ketone bodies, a muscle fuel deficit will also occur.

The other energetic source available to muscle in the presence of a carnitine limitation of long chain fatty acids and inadequate plasma supplies of ketone bodies is from oxidation of amino acids. Of these muscle can most readily oxidize the essential branched chain amino acids but can probably oxidize several others under conditions of need. Since it cannot alter tryptophan, proline, arginine, and ornithine, then to the extent it oxidizes amino acids derived from its own protein it may be expected to release these amino acids. Since muscle can obtain energy from the glycolytic cycle it might also be expected that if the generation of ATP from these other sources was inadequate that it might activate the glycolytic cycle with release of lactate. If this occurs several changes will occur which may be expected to induce muscle capillary and venular vasodilation. Thus a muscle fuel deficit could produce a high cardiac output, the changes consistent on a total body basis with systemic arteriovenous shunting and enhanced lactate gluconeogenesis.

If the preceding occurs with increased consumption of essential branched chain amino acids, unless these are supplied exogenously a progressive limitation of protein synthesis should occur which would be seen first in the liver, gut, and probably pancreas. Albumin is not only a source of colloid osmotic pressure and a transport agent for many bound substances but is also a transport agent for amino acids from the liver to the systemic body.[8] If the muscle fuel deficit limits the supply of branched chain amino acids to the viscera for protein synthesis severely enough, it might be expected that the viscera would clear albumin and utilize the contained amino acids for protein synthesis. Since the branched chain amino acids would be most deficient and hemoglobin has no isoleucine and albumin very little isoleucine, this would be a very inefficient process in which large quantities of albumin might be consumed and in which the associated administration of blood would not help at all.

One might, therefore, expect as the first clinically available sign of a muscle fuel deficit hypoalbuminemia and as later signs a generalized restriction of protein synthesis which would be seen first in those areas with the most active protein synthesis and especially those areas where

immediate function depends upon immediate protein synthesis such as cellular immunity. Thus hypoalbuminemia and cellular immunity should be tied together in time as is observed to happen.[13]

RESULTS

Plasma albumin versus exogenous albumin and exogenous amino acids.

Case 1. Pure Albumin Support

Patient 1 (a 21-year-old male) sustained a severe crushing injury to his pelvis and both upper legs when a lift truck overturned on him and could not be removed for about 1 hour. He immediately went into profound shock when the lift truck was removed. He arrived at this hospital in shock with oliguric renal failure and received 12,000 ml of blood in the first day (Table 1). He had multiple intraabdominal injuries and large areas of dead muscle in the thighs and pelvis. These subsequently became infected presumably secondary to a bacteremia since these were closed injuries and he died on the 24th day. Cardiac output was 16.35 liters per minute acutely and dropped to 9 L.P.M. on day 20. Arterial oxygen tension was maintained in the 100 to 200 mm Hg level throughout his course with ventilatory support and positive and expiratory pressure of 5 cm H_2O with a calculated shunt of 10 to 20 per cent on the ventilator but with poor compliance. Blood volume progressively increased from 6 to 8 liters over the course. BUN ranged up to 276 mg per cent in spite of repeated dialysis.

Results

The plasma albumin ranged between 2.4 and 4 gm per cent with most values in the 2.4 to 3.4 gm per cent range with 10 out of 16 determinations less than 3 gm per cent. This occurred in the face of an average daily albumin administration of 145 gm. Administration of 50 gm per day of amino acids starting on day 10 seemed to make no difference. Starting on day 11 increasing quantities of exogenous albumin were required to maintain the same plasma albumin with the average for the last 7 days being 162 gm per day.

Comment

The overnight fasted rate of albumin production is in the range of 10 to 12 gm per day in association with an hepatic ketone body output of 9 to 45 gm per day and an increased plasma fatty acid.[7, 19] Clearly hypoalbuminemia occurs in these cases in spite of administration of exogenous quantities of albumin grossly in excess of the normal rates of albumin synthesis. The grossly elevated bilirubin in association with increased alkaline phosphatase and fairly normal SGOT and SGPT is typical of this problem.

Table 1. *Case 1 Data*

DAY OF HOSPITAL COURSE	CARDIAC OUTPUT/ ARTERIOVENOUS OXYGEN DIFFERENCE	BLOOD VOLUME/ CENTRAL VENOUS PRESSURE	ARTERIAL PRESSURE	PULMONARY ARTERY PRESSURE/ POSITIVE END EXPIRATORY PRESSURE	INSPIRED OXYGEN FRACTION/ ARTERIAL OXYGEN TENSION	CALCULATED PULMONARY ARTERIOVENOUS SHUNT	ALBUMIN	BLOOD GLUCOSE HIGH/LOW	BILIRUBIN/ ALKALINE PHOSPHATASE	SGOT/SGPT	TEMPERATURE HIGH/LOW	WBC	AVERAGE EXOGENOUS ALBUMIN GM PER DAY	AVERAGE EXOGENOUS AMINO ACIDS GM PER DAY
5	16.35/38	–/7	130/80	–/5	0.40/134	0.14	2.6	113/107	3.3/13	790/540	100/99	11	↑ 145 ↓	↑ 50 ↓
11	13.3/22	6.1/8	130/70	–/5	0.35/156	0.14	3.8	260/130	29/35	216/132	102/101	17		
15	–/35	7.2/14	138/50	–/5	0.35/130	0.14	2.5	160/150	37/–	–/–	103/101	16	↑ 162 ↓	
18	9.1/36	5.8/8.2	90/40	–/5	0.40/160	0.12	2.4	80	26/22	40/34	102/100	16		
22	Expired with disseminated intravascular coagulation and excessive bleeding No postmortem examination obtained													

Case 2. Albumin Plus Standard Hyperalimentation

The patient, a 50-year-old male, was in a severe automobile accident and entered the hospital in shock with severe pulmonary failure (Table 2). As he was receiving blood he had a cardiorespiratory arrest just before intubation. He received 7000 ml of blood on the first day. He was found to have a pneumothorax, a ruptured diaphragm, a liver laceration, a spleen laceration, and contusions of the stomach and pancreatic duodenal area. On day 30 he was found to have acalculous gangrenous cholecystitis and died on day 55 with typical multiple systems organ failure.

Cardiac output in this patient ranged on days 2 to 13 from 12 to 16 liters per minute in association with a mean pulmonary artery pressure of 25 to 35 cm H_2O, a right atrial pressure of 15 to 22 cm H_2O, and a positive end expiratory pressure of 8 to 13 cm H_2O. The arterial oxygen tension ranged from 70 to 160 mm Hg with most values above 100 mm Hg on inspired oxygen of 60 to 80 per cent. The blood volumes ranged from 6 to 8 liters over the first 12 days. He was continuously febrile.

Results

On days 2 through 14, he had a plasma albumin in the range of 2.8 to 3.8 with most values in the range of 3 to 3.4 gm per cent with an exogenous albumin intake averaging 87.5 gm per day.

On days 23 through 31 while receiving standard hyperalimentation providing an average 100 gm of amino acids per day, the plasma albumin was in the range of 2.8 to 3.4 with most values 3.0 gm with an average exogenous albumin intake of 51.4 gm per day.

On days 43 through 52, the plasma albumin ranged between 1.8 and 3.0 with most values in the 2.4 to 3.0 gm per cent range in association with 100 to 125 gm of amino acids per day plus 62 gm of exogenous albumin per day.

Comment

Exogenous amino acids clearly reduce the amount of albumin required to maintain a given plasma albumin. Days 43 through 52 are terminal days for this patient with sepsis. Case 1 required 50 gm of exogenous amino acids and 162 gm of exogenous albumin to obtain a plasma albumin in the 2.4 to 3.4 gm per cent range for a total of 212 gm. This case obtains the same sort of plasma albumin with 62 gm of exogenous albumin plus 100 to 125 gm of amino acids for a total of 162 to 187 gm.

Case 3. Albumin Plus Amino Acids

This very obese 50-year-old lady received a close range shotgun wound of the abdomen with massive destruction of the abdominal wall, small intestine, and right colon, and a ruptured spleen. She had massive bleeding and was in shock for a period of 2 to 3 hours. The small intestine, right colon, and spleen were resected and an ileocolic anastomosis was done. She developed multiple and recurrent intraabdominal abscesses,

Table 2. *Case 2 Data*

DAY OF HOSPITAL COURSE*	CARDIAC OUTPUT/ ARTERIOVENOUS OXYGEN DIFFERENCE	BLOOD VOLUME/ CENTRAL VENOUS PRESSURE	ARTERIAL PRESSURE	PULMONARY ARTERY PRESSURE/ POSITIVE END EXPIRATORY PRESSURE	INSPIRED OXYGEN FRACTION/ ARTERIAL OXYGEN TENSION	CALCULATED PULMONARY ARTERIOVENOUS SHUNT	ALBUMIN	BLOOD GLUCOSE HIGH/LOW	BILIRUBIN/ ALKALINE PHOSPHATASE	SGOT/SGPT	TEMPERATURE HIGH/LOW	WBC	AVERAGE EXOGENOUS ALBUMIN GM PER DAY	AVERAGE EXOGENOUS AMINO ACID GM PER DAY
8	10.4/50	6.3/18	140/80	30/12	0.50/120	0.15	3.7	/152	5.6/5.1	41/36	103/102	22	87.5	0
23	–/49	/12	130/72	–/9	0.50/97	0.16	2.9	239/217	5.8/4.5	24/39	103/101	32	51.4	100
32	–/26	/15	150/80	–/9	0.50/95	0.25	2.9	276/258	2.7/6.2	58/32	104/101	26		
33	Surgery for acute acalculous gangrenous cholecystitis													
43	–/40	–/16	170/105	–/10	0.70/105	0.19	2.6	279/194	9.2/4.1	88/49	100/100	17	62	125
53	–/28.5	6.6/17	120/50	–/11	0.68/168	0.26	1.7	400/192	7.2/4.2	–/–	102/99	11		

*Day 33—Stress ulcer bleeding from stomach by gastroscopy. Multiple episodes of stress ulcer bleeding recurred episodically.
Day 55—Death with bleeding and ventricular arrhythmias.
Postmortem—Peritoneum—Mild fibrinous peritonitis.
Heart—Cardiomegaly (550 gm) with dilatation.
Liver—Hepatomegaly (3600 gm) with cirrhosis and marked icterus.
Lungs—Bilateral pulmonary edema with pneumonia and pleural effusion
Gut—Acute mucosal ulceration with multiple superficial erosions.

principally pelvic and subdiaphragmatic, in association with multiple intestinal fistulae. Terminally she developed a left empyema. She had multiple operative procedures and expired on the 68th day with typical multiple systems organ failure. She was always febrile, but had positive blood cultures only on the last 10 days. Her pulmonary function on the ventilator with 5 cm of positive end expiratory pressure produced an arterial oxygen tension above 100 on 40 per cent oxygen at all times except terminally. This case was not studied intensively in terms of cardiopulmonary function.

Results

Periods of circulatory crisis have been omitted. On days 2 through 14 the plasma albumin was in the 3.8 to 4.0 gm per cent range in association with an average of 125 gm of amino acids and 24 gm of exogenous albumin per day.

On days 19 through 43 the plasma albumin was in the range of 3.5 to 4.2 with an average intake of 47.6 gm of albumin and 250 gm of amino acids per day. On days 43 through 58 the plasma albumin was in the range of 3.8 to 4.6 with most values above 4 gm per cent in association with an average of 60 gm of exogenous albumin per day and an average of 185 gm of amino acids per day.

Comment

The first period illustrates the trauma adaptive phase in which minimal quantities of exogenous amino acids and albumin are required to maintain the plasma albumin. This period was associated with ketonuria. The second and third periods illustrate in the patient who is receiving intensive cardiopulmonary support the point that sepsis is associated with a gross increase in the requirement for exogenous amino acids and albumin to maintain the plasma albumin. This case may be compared with Case 1 where hypoalbuminemia occurred in spite of 162 gm of albumin per day in association with 50 gm of amino acids per day.

Comment—Case Material on Plasma Albumin

These cases are illustrative of several cases with the common theme that sepsis is associated with the need for far greater quantities of amino acids and albumin to maintain the plasma albumin than is required for normal man. These observations are associated in time with the observations in the literature that greater quantities of nitrogen and calories are required to achieve nitrogen balance in septic man than in normal man and with the observation that septic man burns a fuel mixture with a more reduced caloric to nitrogen ratio (75 to 150) than starved man (400 to 600).[4] These observations are routinely associated with high cardiac outputs and good arterial pressures and under conditions of ventilatory support with arterial oxygen tensions well above those that might limit metabolic function.[5]

CASE 4

Clinical Data

This 21-year-old male drove his car 225 feet in a ditch until it struck a culvert and careened 75 feet. Extraction from the car required 1 hour. He arrived in shock with a massive pelvic injury, intraabdominal bleeding, and a myocardial contusion. The pelvic injury involved not only a severely shattered pelvis, but also bilateral dislocation of the hips with central protrusion acetabular fractures. A laparotomy revealed only multiple areas of contusion and a massive pelvic hematoma with bleeding from all raw surfaces. When the wound had just been closed there was massive bleeding from the wound. The wound was then re-opened and again only oozing from all raw surfaces was found. The patient was in and out of shock repeatedly in the first 2 days and received 17,125 ml of blood, plasma, and fresh frozen plasma the first day plus 6000 ml of similar fluids the second day. In spite of these fluids and diuretics, he promptly went into oliguric renal failure. The bladder area was examined at laparotomy and with three subsequent cystograms, all of which were negative. On the twenty-third hospital day a laparotomy for a bowel obstruction revealed a massive pelvic abscess with a free communication to the bladder. The patient was continuously febrile with a leukocytosis, but had 30 negative blood cultures. The following represents only a partial analysis of the data. A complete analysis with multiple statistical correlations and statistical analysis for significance will be published separately.[14, 15]

Cardiopulmonary Data

Cardiac outputs were done on days 2 to 4, days 8 to 10, and days 15 through 20. The cardiac outputs ranged from 3 liters per minute to 12. The cardiac outputs in the initial period began at 11.4 and ended at 6.8 liters per minute. The cardiac output in the middle period ranged from 4.3 to 6.8 liters per minute with only one value below 5 liters per minute. The cardiac outputs in the last period ranged from 3.2 to 12.4 liters per minute with 11 out of 14 values of 5 or greater. Blood volume ranged from a low of 5 liters to a maximum of 7.8 liters, with most values in the range of 6 to 7 liters. Arterial pressure was in the normal range, except for periods of crisis originally and terminally and was associated with a right atrial pressure of 5 to 25 cm H_2O, with most values in the range of 10 to 20 and terminal values in the range 20 to 30 cm H_2O. Positive end expiratory pressure of 5 cm H_2O in association with a volume cycled ventilator was continuously applied. This was associated on inspired oxygens of 40 to 50 per cent with arterial oxygen tensions in the range of 80 to 150 mm Hg and a calculated shunt which ranged from 10 to 40 per cent, with most values in the range 10 to 20 per cent. BUN rose to a maximum of 170 mg per cent.

The Study

The patient was left on clinically indicated support 16 hours out of each day with the plan that 2-hour infusions of saline, 10 per cent glucose, 2.69 per cent amino acids, and 8.5 per cent amino acids would then be performed with blood samples from an hepatic vein catheter and arterial

catheter at the beginning of the day and after each infusion. Clinical management problems allowed the basal samples to be collected on most days, but allowed only 2.69 per cent amino acid infusion plus saline infusions on days 9, 10, and 12 and 8.5 per cent amino acid infusion, 10 per cent glucose, and saline infusion studies on days 17, 18, and 20. No studies were conducted on days of hemodialysis or clinical crisis. The clinical course of the patient may be divided into the shock phase days 1 and 2, the shock adaptive phase days 3 through 5, the trauma adaptive phase days 5 through 10, and the septic phase days 10 through 21 with its subdivision, the late septic phase days 17 through 21.

Metabolic Data

HORMONES. The plasma insulin was fixed below fasting levels (5 to 10 micro units per ml) and unresponsive to exogenous glucose and amino acids. The plasma glucagon was at all times considerably above normal but was very high in the first 5 days (1000 pgm per ml) and then drifted down to a high plateau (400 to 600 pgm per ml) for the remainder of the course. The glucagon was also unresponsive to exogenous glucose and amino acids. The plasma cortisol was very high initially (300 to 500 mcg per ml) but fell to the normal range by 5 days (100 to 200 mcg per ml) and remained there.

ALBUMIN. The plasma albumin remained in the range of 3 to 4 gm per cent in the first 10 days in association with exogenous albumin which averaged 50 gm per day on days 3 through 5, and 43 gm per day on days 5 through 10 (trauma adaptive phase). In the septic phase the plasma albumin ranged from 2.8 to 3.6 gm per cent with an exogenous albumin which averaged 59 gm per day on days 11 to 18 and 75 gm per day on days 19 to 21. No amino acids were given to the patient and the background support other than albumin was 5 per cent glucose.

Basal Studies

PLASMA SUBSTRATES CONCENTRATIONS. A paired "t" test between the average values of the plasma substrates obtained after basal 5 per cent glucose support and saline infusion on days 5, 9, 10, and 12 revealed no significant differences except for glucose, Pco_2, and bicarbonate. These data were therefore pooled to increase the basal data pool.

A comparison of this averaged pooled data to the results obtained with identical analytic procedures on six overnight fasted normals revealed that the plasma concentrations of isoleucine, lysine, threonine, serine, glycine, alanine, ornithine, histidine, and arginine were significantly less than normal, while tryptophan, phenylalanine, lactate, free fatty acids, glucose, and triglycerides were significantly greater than normal at the $P = 0.05$ level. The amino acids present in lowest concentration in order of rank were isoleucine, lysine, and threonine, while tryptophan was present in relatively higher concentrations than phenylalanine.

Comment 1. The albumin and blood support is relatively deficient in isoleucine. The particularly low concentrations of isoleucine are therefore to be expected. Albumin is even more deficient in tryptophan (1 per molecule). The high tryptophan would not be expected on the basis of albumin support.

The tyrosine to phenylalanine ratio was significantly reduced, while the ratio of tryptophan to large neutral amino acids (phenylalanine + leucine + valine + isoleucine + tyrosine) was significantly increased ($p \leq 0.005$).

Comment 2. The high phenylalanine and low tyrosine imply inadequate hepatic conversion of this amino acid. The high tryptophan to large neutral amino acid ratio implies increased brain serotonin and is compatible with hepatic coma. The low tyrosine is compatible with inadequate production of norepinephrine.[10] These measurements imply altered neuroendocrine control of metabolism and cerebral function.

The plasma concentrations of several substrates varied together. Group I included many substrates which began at a minimum, reached a maximum on days 5 to 10, and then approached a minimum on day 20 to 21. Group I substances included threonine, serine, proline, methionine, isoleucine, leucine, tyrosine, ornithine, lysine, histidine, BUN, acetoacetate, beta hydroxybutyrate, and triglycerides. Group IIa substances changed in an entirely opposite way as a function of time and had a minimum about day 10. The Group I substances of dominant influence as judged by statistical correlations (number of correlations at $p \leq 0.05$) included acetoacetate, BUN, histidines, and triglycerides. The Group IIa substances included lactate, pyruvate, alanine, and glutamine. All correlations in this group were at $p \leq 0.05$. These plus glucose, pH, and bicarbonate constituted the Group II substances.

The Group II substances were maximal and the Group I substances plus all amino acids were minimal in the shock phase. The Group I substances were maximal and the Group II substances minimal at the junction of the trauma adaptive phase and the septic phase (day 10). At the end of the septic phase the Group IIa substances had again become dominant and the Group I substances minimal.

Comment 3. These concentration changes are consistent with the shock and late septic phases, being ones of glucose oxidation and anaerobic metabolism, while the shock adaptive and trauma adaptive phases are ones of increasing fat oxidation and the septic phase one of decreasing fat oxidation.

PLASMA SUBSTRATE AND SPLANCHNIC BALANCES. The first 8 days of the patient's course are ones of increasing plasma free fatty acids (700 to 2000 micromoles per liter), and ketone bodies (30 micromoles to 590 micromoles per liter).

The splanchnic balance studies in this period show a constant output of ketone bodies (89 micromoles per liter) and increasing clearance of free fatty acids (50 to 300 micromoles per liter).

Comment 1. The increasing plasma ketone bodies in association with an unchanged splanchnic output and increasing plasma free fatty acids, suggest that this is a phase of increasing systemic oxidation of long chain fatty acids. It is of some interest, therefore, that direct measurement shows it to be a period of increasing splanchnic free fatty acid clearance.

The onset of the septic phase probably begins between days 8 and 10. The plasma free fatty acids drop in this period from 2000 to 1200 micromoles per liter and then drop further on days 10 to 20 to 1100 micromoles. The plasma acetoacetate drops from 270 micromoles per liter

on day 10 to 80 micromoles on day 17. The splanchnic clearance of free fatty acids (300 micromoles per liter) and output of ketone bodies (89 micromoles per liter) is unchanged in this period. The splanchnic clearance of free fatty acids decreases from day 17 to 20 (300 to 200 micromoles per liter) as the splanchnic clearance of proline increases (225 to 350 micromoles per liter) and the clearance of a grossly unbalanced mixture of amino acids rapidly increases. This period is also associated with an increasing plasma lactate (1200 to 2000) and pyruvate (80 to 160), but an unchanged lactate to pyruvate ratio of 15.

Comment 2. The decreasing plasma ketone bodies on days 10 to 17 in association with an unchanged splanchnic output and decreased but relatively stable free fatty acids is compatible with decreasing systemic oxidation of free fatty acids. The splanchnic clearance of free fatty acids suggests that this does not involve in a measurable way the liver until it is required to clear large amounts of an unbalanced amino acid mixture beginning on day 17.

At about days 8 to 10 with the onset of the septic phase, a large number of changes occur. At this time the plasma concentration of the following rapidly rises: aspartate—12 to 50 micromoles per liter, glutamate—20 to 65 micromoles, and alpha amino butyrate—8 to 30 micromoles. In this same period the splanchnic system goes from releasing small amounts of glutamate plus aspartate to releasing large amounts (change in negative fractional clearance from 0.2 to 0.65). At the same time as the increased release of aspartate and glutamate the splanchnic system ceases clearing alanine and glutamine and begins to clear increasing amounts of the amino acids tryptophan and proline. Alanine clearance remains at zero to plus 25 micromoles per liter for days 10 to 20 in the basal state while glutamine clearance for the same period is zero or a release of about 20 micromoles occurs. Tryptophan clearance increases from zero to plus 9 micromoles per liter while proline clearance goes from zero to plus 350 micromoles over the same period of days 10 to 20. In this same period the plasma ammonia increases from 250 to 350 micromoles per liter.

Comment 3. Beginning on days 8 to 10 there are several signs of decreased systemic body free fatty acid oxidation. At the same time the following occurs:

1. Increased splanchnic clearance of two amino acids, tryptophan and proline, that muscle cannot alter.
2. Increased splanchnic release of the amino acids aspartate and glutamate which muscle can probably use for energy.
3. Decreased splanchnic clearance of alanine and glutamine which muscle uses to transport nitrogen and in whose muscle metabolism aspartate and glutamate are very important.
4. An increase in plasma ammonia and its splanchnic clearance.

The increased splanchnic clearance of proline and release of glutamate may be related since glutamate is a metabolite of proline. The splanchnic system would thus be able to convert an amino acid muscle cannot metabolize to one it can metabolize in exactly the same way muscle normally metabolizes the branched chain amino acids and thus produces alanine and glutamine while gaining energy itself.

The splanchnic clearance of isoleucine is progressively reduced with time from a day 2 value of 12.5 micromoles per liter to a day 17 value of zero. The same reduction in clearance with the same order of magnitude change occurs for methionine. These are statistically significant changes. These data may be restated and enlarged. The average splanchnic clearance of the summed branched chain amino acids which muscle clearly can oxidize is 59 micromoles per liter on days 3 to 5, 43 micromoles per liter on days 5 to 10, and 12 micromoles per liter on days 10 to 20.

If one adds to the branched chain amino acids aspartate and glutamate which muscle can probably oxidize, then the summed average splanchnic clearance on days 3 to 5 is 42 micromoles per liter, 26 micromoles on days 5 to 10, and the splanchnic system releases a summed average of 14 micromoles per liter on days 10 to 20.

Comment 4. By any measure with the passage of time the splanchnic system clears progressively less of the amino acids muscle can utilize for energy. The branched chain amino acids cannot be catabolized by the splanchnic system and may therefore be utilized as an index of protein synthesis. By this index the shock adaptive phase is a period of maximum splanchnic protein synthesis, the trauma adaptive phase is one of somewhat reduced (59 to 43 micromoles branched chain amino acid clearance) but still high protein synthesis, and the septic phase (12 micromoles clearance) one of low splanchnic protein synthesis.

These measurements appear well reflected in the exogenous requirements for amino acids and albumin to maintain the plasma albumin. It is of considerable interest that the progressive reduction in splanchnic isoleucine clearance is not attended by a significant further drop in plasma isoleucine concentration or an alteration in splanchnic fractional clearance.

The amino acids muscle cannot alter and releases when consuming amino acids from its own protein are tryptophan, proline, arginine, and ornithine. The progressive increase in tryptophan and proline clearance beginning day 10 has already been described. The summed splanchnic clearance of these amino acids is 60 micromoles on days 3 to 5, 22 micromoles on days 5 to 10, and 229 micromoles per liter on days 10 to 20.

Comment 5. The splanchnic system clears the greatest quantity of both branched chain amino acids and these amino acids on days 3 to 5. These two sets of observations both show this to be a phase of maximal splanchnic protein synthesis. The clearance of 22 micromoles per liter of these summed amino acids plus 43 micromoles per liter of branched chain amino acids on days 5 to 10 suggests that on days 5 to 10 the splanchnic system receives the best balanced mixture of amino acids while still preserving most of its protein synthesis. The period from days 10 to 20 is one in which the splanchnic system receives a maximally unbalanced mixture of amino acids and has the least protein synthesis. This should be a period of maximum ureagenesis.

The maximal splanchnic protein synthesis on days 3 to 5 and high protein synthesis on days 5 to 10 probably reflect primarily release of a balanced mixture of amino acids from muscle secondary to the sudden onset of physical rest in previously active muscles and the high plasma

cortisol in association with the low plasma insulin. The maximally unbalanced amino acid mixture cleared by the splanchnic system between days 10 and 20 probably reflects a muscle fuel deficit which induces branched chain amino acid consumption. This is probably also reflected in the requirements for large amounts of exogenous amino acids to obtain a normal plasma albumin.

INFUSION STUDIES AND SPLANCHNIC BALANCES

On the preceding basal background infusion studies of amino acids were carried out. A balanced amino acid mixture for normal man was infused for 2-hour periods at a daily rate of 91.8 gm on days 9, 10, and 12 and for 2-hour periods at a daily rate of 306 gm on days 17, 18, and 20. This solution was found to be tryptophan-free by analysis. Tryptophan is unstable in solution.

The most interesting observations for this paper are that the splanchnic system cleared the amino acids infused in proportion to their increased concentration except for isoleucine which it cleared preferentially to the other branched chain amino acids at the low amino acid infusion rate (38 vs. 21 per cent). This observation was associated with tryptophan clearance going from a day 10 value of zero to 8 ± 14 and with the splanchnic albumin clearance going from the average basal value of 23 ± 56 to 8 ± 8 micromoles per liter clearance. At high amino acid infusion ratio on days 17, 18, and 20 the splanchnic clearance of branched chain amino acids generally increased relative to the average basal state and the day 18 value for isoleucine and again the splanchnic clearance of albumin decreased relative to the average basal value (23 ± 56 to 3 ± 4).

The splanchnic clearance values may best be interpreted by comparison to the infusion rates. This is best done with the assumption that the splanchnic blood flow is equivalent to 1000 ml of plasma water per minute. Granted this assumption at the low amino acid infusion rate, 31 per cent of the infused branched chain amino acids were cleared by the splanchnic system in association with 77 per cent of all other infused essential amino acids, 100 per cent of the infused threonine, 250 per cent of the infused lysine, and 127 per cent of the infused nonessential amino acids. Thus the systemic body cleared 69 per cent of the infused branched chain amino acids, received no threonine, lost lysine, and lost nonessential amino acids to the splanchnic system. The increment in infused branched chain amino acids cleared by the periphery was 81 micromoles per minute. The observed increment in splanchnic clearance of alanine and glutamine and ammonia beyond the basal and infusion rate was 64 micromoles per minute. It should be noted that these studies were conducted when the basal alanine and glutamine splanchnic clearances were zero.

The high amino acid infusion studies were conducted in the late septic phase when maximal requirements for exogenous amino acids and albumin exist. Under these conditions 48 per cent of the infused branched chain amino acids were cleared by the splanchnic system in association

with 69 per cent of all other essential amino acids infused plus 100 per cent of the infused lysine, 85 per cent of the infused threonine, and 76 per cent of the infused nonessential amino acids. The systemic body under these conditions clears 195 micromoles per minute of the infused branched chain amino acids plus 173 micromoles of nonessential amino acids other than proline while the splanchnic system clears an increment above the basal and infusion rates of 249 micromoles of alanine glutamine and ammonia. This increment contains 144 micromoles of alanine and 93 micromoles of ammonia and only 12 micromoles of glutamine and occurs on the background of zero splanchnic alanine clearance and zero clearance or release (25 micromoles) of glutamine. If glutamine is actually being released at a rate of 25 micromoles per minute in the basal state, then the increment in clearance would be 274 micromoles per minute instead of 249.

The behavior of proline, arginine, and ornithine with amino acid infusion is clearly special. Thus on day 18 the basal proline clearance is 350 micromoles per liter, the infusion rate is 205 micromoles, and the observed clearance with infusion is 30 micromoles per liter. The average basal clearance of arginine is 20 micromoles per liter, the infusion rate is 46 micromoles per liter, and the observed clearance 40 micromoles per liter. Ornithine is not infused. The average basal clearance is 7 micromoles per liter while with infusion it releases 1 micromole per liter.

COMMENT. The splanchnic system can clear branched chain amino acids when they are infused and does so in association with a reduced clearance of albumin and enhanced clearance of several other amino acids. These observations are compatible with protein synthesis. As a first approximation the hepatic dysfunctions observed, including the hypoalbuminemia, must be viewed as secondary to an inadequate supply of branched chain amino acids from the periphery. Granted the persistent albumin clearance in the basal state by the splanchnic system and its reduced clearance with amino acid infusion as a first approximation, we must assume that in the presence of inadequate branched chain amino acid supplies to the splanchnic system that it clears and breaks down albumin as an alternate amino acid source. Unfortunately, albumin is very poor in isoleucine, one of the deficient amino acids.

The systemic body clears with infusion an amino acid mixture rich in branched chain amino acids, devoid of lysine and threonine, and very poor in the other essential amino acids. This mixture cannot be used for protein synthesis and it is not surprising that all or almost all of the nitrogen so cleared can be accounted for as alanine glutamine, and ammonia clearance by the splanchnic system. The restricted clearance increment of glutamine with high amino acid infusion on days 17, 18, and 20, together with enhanced clearance of ammonia, strongly suggests some fundamental limitation of glutamine synthesis. The alanine clearance from day 10 to 20 is essentially zero; however, the infusion experiments show that alanine can still be synthesized if branched chain amino acids are exogenously provided.

The preceding infusion studies also show that the splanchnic system clears an amino acid mixture rich in all amino acids except the branched

chain amino acids. This same observation is also made in the basal state in the septic phase. The amino acids in excess of the protein synthesis allowed by the branched chain amino acids can only be catabolized with production of urea and glucose.

These observations are best put together as resulting from a muscle fuel deficit as specifically described in the section entitled hypothesis. This would necessarily involve a carnitine limitation of long chain fatty acid oxidation granted the plasma free fatty acids and probably a limitation of the lipoprotein lipase ability to liberate fatty acids from triglycerides and the splanchnic synthesis of lipoprotein. It has not been described, but the splanchnic system consistently cleared triglycerides and never released them.

The splanchnic output of ketone bodies was consistently 6 to 8 gm per day. 91.8 gm of amino acids provides 20.7 gm of branched chain amino acids. Thus, in a patient on 91.8 gm of amino acids per day, there are only 27 to 29 gm of carnitine independent muscle fuel. If the patient were receiving 306 gm of amino acids per day, and had this same ketone body output, then there would be 69 gm of carnitine independent muscle fuel. This may be compared to an overnight fast where carnitine is abundantly present and the ketone bodies provide 9 to 45 gm of such fuel and to a 3 day fast where the ketone bodies provide roughly 125 gm of carnitine independent muscle fuel.

Clearly, if there is a significant carnitine limitation of long chain fatty acid oxidation, the amounts of carnitine independent muscle fuel provided are grossly inadequate. Further, this produces a grossly unbalanced amino acid mixture where all nitrogen provided would be converted to urea and may well produce toxic plasma concentrations of the essential amino acids muscle cannot utilize unless sufficient hepatic protein enzymes are induced to destroy these other amino acids at the rate they are infused.

This problem is well exemplified in Case 3 where the large amounts of amino acids which were given were associated with good plasma albumins even in the late septic phase and normal branched chain amino acid concentrations but were also associated with a tryptophan 3 to 6 times normal, a methionine 24 to 30 times normal, and a phenylalanine 2 to 3 times normal. Another patient who was shot through the heart and eventually died of pneumonia while receiving the same amounts of amino acids via the gastrointestinal tract, had very low concentrations of all amino acids except methionine which was only 1.5 to 2.0 times normal. In association with this, not only was his plasma albumin in the 3.4 to 5.2 range with 5 out of 10 values above 4 gm per cent, but also his retinol binding protein was maintained in the range of 1 to 2 times normal in all observations.

The essential changes of prolonged sepsis in these chronically and critically ill patients, by consuming branched chain amino acids, cause a balanced amino acid mixture for normal man to be an unbalanced amino acid mixture for septic man in that the mixture is relatively deficient in branched chain amino acids and has a relative excess of all other essential amino acids. This is reflected very well in patient 3 in terms of amino acid

concentrations. If one must give an amino acid mixture which has for the total body a relative excess of those amino acids consumed by the liver, this is much better given via the gastrointestinal tract so that the liver may most effectively consume those particular amino acids. This is also the route which most effectively stimulates splanchnic protein synthesis including not only the liver but also the gastrointestinal mucosa.

DISCUSSION AND SUMMARY

The data confirm that with severe prolonged sepsis much greater quantities of exogenous albumin and amino acids are required to maintain a normal plasma albumin. The case studied in detail is best interpreted as having limited splanchnic protein synthesis secondary to an inadequate supply of branched chain amino acids. The changes associated with this are most compatible with a muscle fuel deficit secondary to: (1) a carnitine limitation of long chain fatty acid oxidation; (2) limited lipoprotein synthesis; (3) limited muscle availability of triglyceride fatty acids; and (4) limited hepatic output of ketone bodies. If such a muscle fuel deficit is present it will not be improved by administration of intravenous lipids which are long chain fatty acids and will be made worse by intravenous glucose to the extent that the glucose interferes with hepatic ketone body output.

The data also show that administration of large enough intravenous quantities of a commercially available amino acid mixture to return the plasma branched chain amino acids to normal is associated not only with evidence compatible with albumin and retinol binding protein synthesis, but also with toxic concentrations of the essential amino acids other than the branched chain amino acids. This is particularly true of methionine which was 24 to 30 times the normal concentration. This did not occur except for methionine at a value three times normal when the amino acids were administered via the gastrointestinal tract. Clearly large quantities of amino acids are best administered via the gastrointestinal tract not only because of the toxic amino acids effects but also because of the selective increase in gastrointestinal and hepatic protein synthesis which probably also occurs. It is of considerable interest that methionine, a carnitine precursor, is the amino acid that increases the most in concentration.

If a carnitine limitation of long chain fatty acid oxidation really does contribute significantly to a muscle fall deficit which then eventually limits protein synthesis throughout the body, then no presently available method of therapy is acceptable. The use of conventional hyperalimentation in this sort of patient will buy some time by virtue of the branched chain amino acids provided but will make things worse in two ways. One is the limitation of hepatic ketogenesis and the second is the production of a fatty liver which may interfere with hepatic blood flow and therefore all hepatic synthetic processes. This will occur to the extent the infused glucose stimulates hepatic glucose lipogenesis in excess of the capacity for lipoprotein synthesis for transport of the excess triglycerides from the liver to the systemic body. The prolonged use of pure glucose by interfer-

ing with hepatic ketogenesis and not supplying branched chain amino acids is highly likely to induce muscle consumption of branched chain amino acids and thus induce a generalized limitation of protein synthesis which has hypoalbuminemia as its first manifestation.

Proper therapy for the muscle fuel deficit might include administration of carnitine but would surely include administration of a carnitine independent muscle fuel. There are no such fuels available today except for the ketone bodies. However, since they must be given as the sodium or potassium salts and are metabolized to bicarbonate, the amount that can be administered is very limited. We have been working for some time now on development of such fuels. A carnitine independent muscle fuel would include a fatty acid eight carbons or shorter which for electroneutrality should be coupled to another oxidizable compound in a way that the coupling could be readily lysed in the body. We have so far investigated the monoglycerides of butyric acid and of acetoacetate.[2, 3] Rats can clearly be supported on these compounds intravenously for 10 to 14 days without apparent toxic effects and while gaining weight normally. Another such compound of interest if the gastrointestinal tract can be utilized are the medium chain triglycerides since they are 70 per cent eight carbon fatty acids and less and simultaneously induce hepatic ketogenesis. Thus, they could be oxidized as a carnitine independent muscle fuel either directly or indirectly as ketone bodies.

It is of some interest, granted the rather complicated evidence required to produce the concept of a muscle fuel deficit limiting splanchnic protein synthesis, that any mother could have told us many years ago that too much candy for too long was bad for her children. Our prized intravenous glucose is basically candy. Any Jewish mother could have told us her sick children were better with chicken soup. Carnitine is heat stable and therefore contained in chicken soup. Tryptophan and lysine are heat labile and therefore destroyed in chicken soup and the branched chain amino acids are stable and therefore preserved. In addition, since it contains no glucose and is given under fasting conditions, hepatic ketogenesis should occur and finally it provides the salt and water clearly needed. Thus, all of the complicated evidence presented basically supports what any mother could have told us years ago.

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Energy Metabolism and Proteolysis in Traumatized and Septic Man

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Proteolysis for energy production by oxidation of amino acids has been recognized since Cuthbertson's observations[14] as characteristic of serious injury and infection. Failure of protein synthesis[20] in turn leads to weakness, loss of immunocompetence, hypoalbuminemia, and failure to heal wounds. If not arrested by elimination of the stimulus or by adequate alimentation, the ultimate results are further infection, multiple organ failure, and death. This state of affairs contrasts with the economic pattern of protein sparing observed following adaptation to normal starvation in which body fat stores are primarily mobilized to furnish energy essential for the functions of vital organ systems.[6]

Kinney and his colleagues[17, 29, 31] recognized that under these conditions not only is glucogenesis increased but that the body glucose pool is increased. Paradoxically, the administration of glucose fails to reduce the excessive glucogenesis.[5, 22] Since the observations of Howard[25] on wounded personnel in Korea it has been known that insulin resistance exists in injured and septic patients. Dr. Ryan in a preceding paper of this symposium has outlined the evidence for the presence of an energy fuel deficit established by an insulin resistance in muscle. Dr. Wilmore further has described the interrelationship of the function of various organ systems and the endocrines, while Dr. Border has related failure of protein synthesis to a deficit of certain essential amino acids.

The purpose of this article is to present evidence from clinical studies of trauma and sepsis which support the view that alterations of peripheral energy metabolism, particularly by insulin resistance in skeletal muscle,

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causes proteolysis, excessive glucogenesis, and, ultimately, failure of protein synthesis. Furthermore, from studies employing bioassays it appears that, in addition to the effects of catecholamines and steroids, muscle insulin resistance is established by one or more circulating agents (probably peptides).[9]

The disturbance of metabolism and the degree of proteolysis is proportional to the extent of injury both local and to cells in general throughout the body. To emphasize this relationship three clinical states are compared with the pattern of normal fasting: (1) *Convalescence from clean surgical operations* which represent moderate noninfected trauma, (2) *Severe sepsis with high cardiac output*, the usual pattern of recovery, and (3) *Sepsis associated with low cardiac output*, insufficient to satisfy circulatory demands, commonly called "shock." In order to clarify these clinical situations the physiologic state of each will be presented before proceeding to a description of the utilization of body fuels in each, since the metabolic abnormalities in each are intimately related to alterations of the normal physiologic pattern.

THE POST-TRAUMATIC AND SEPTIC COURSE

Contrasting with the benign convalescence from clean major surgery is the febrile, sometimes hectic, response of the injured patient in whom inflammation, gangrene, or infected tissue is present. The protective physiologic and immunologic responses are all organized for maintenance of cellular metabolism and for limiting the spread of infection and injury to cells. The responses of various organs, particularly the cardiovascular system, are under dual control of both local factors as well as the central nervous system, the latter being largely mediated through the autonomic nerves and endocrines. For convenience, the post-traumatic and septic course can be divided into three phases: (1) *Tissue injury and bacterial invasion*, (2) *Localization* of the gangrenous or septic process, and (3) *Resolution and recovery*. It is important to realize that these are not clearly identifiable conditions but that they merge. Furthermore, it is possible to revert from one phase to another.

In the early stage of *injury and bacterial invasion*, life is maintained by the protective physiologic responses while immunologic and inflammatory reactions isolate the process. Early death often appears as circulatory failure and shock, but in fact is usually associated with complete disruption of energy production in certain vital organs such as the liver and even the cardiovascular system itself. Subsequently, during the phase of *localization*, many stresses remain. Not only are the functions of major systems impaired, for example, the gastrointestinal tract in peritonitis, but toxic products continue to enter the circulation by diffusion into the lymphatics and capillaries. These act directly or indirectly upon the cells of distant organs. Late deaths are usually caused by respiratory failure as well as by insufficiency of other organs. Often death is attributable to severe nutritional depletion. Proteolysis and failure of protein synthesis lead both to weakness and to loss of immunocompetence.

Finally, *resolution* of the gangrenous or septic process by sloughing of necrotic tissue or drainage of pus will lead to healing. Recovery is completed by the restoration of tissue depleted by metabolic demands, first by protein synthesis and subsequently by deposit of fat in adipose tissue.

Uneventful Surgical Convalescence

The data presented in Table 1 emphasize the highly significant physiologic differences between uneventful convalescence and posttraumatic or septic states. Virtually no abnormal circulatory demands are imposed. The average maximal pulmonary shunt is only 12 per cent, resulting in no significant hypoxemia, and the metabolic rate is only slightly above normal. The average maximal cardiac index immediately postoperative is 3.6 L per M^2 per min compared with a normal value of 2.8 L per M^2 per min. Subsequently it remains near 3.0 L per M^2 per min.

High Output Trauma and Sepsis

On the other hand, in injured, and especially in infected patients, the metabolic rate as measured by partition calorimetry[49] rises to values between 20 and 35 per cent above normal, findings similar to those previously observed by Kinney and his colleagues.[28, 29] In patients who recover following trauma or the onset of sepsis, the cardiac index is usually elevated 50 to 95 per cent above normal. This discrepancy between the elevation of metabolic rate and that of the cardiac output suggests the presence of an inappropriate peripheral vasodilation. Clinical observations and experimental data indicate that in the high output state augmented blood flow occurs secondarily to reduced resistance in the inflammatory area,[1] the kidneys,[40] and the splanchnic bed.[23] Recent evidence from the study of septic patients and animals demonstrates that the flow in extremities is increased proportionately to the elevation of the cardiac output.[19, 36] A number of explanations for the apparent general vasodilation and continued large circulatory demand have been suggested: (1) The possibility exists that microanatomic shunts may open in the mesentery, in the skin, and in other tissues. However, Wright et al.[53] found a highly significant correlation between the muscle capillary flow and the extremity flow using xenon 133 clearance. (2) A more likely cause is that vasodilator substances activated by tissue injury or endotoxin may be responsible. Cross perfusion experiments by Hermreck and Thal[23] demonstrated that venous blood drained from the infected sites was capable of reducing vascular resistance in normal tissues. Experimental infusion of nonprotein plasma fractions from septic animals or patients into the artery of an extremity in our laboratory also produces vasodilation not observed with normal fractions. (4) Alternatively, the demand for increased circulation may be the result of cellular metabolic abnormalities, either due to impairment of oxygen delivery or excess vasodilator metabolites. Siegal et al.[47] have drawn attention to the reduced venous extraction of oxygen from circulating blood and the high oxygen content of mixed venous blood. A shift to the left of the oxyhemoglobin dissociation curve, as occurs in alkalosis or when 2–3 DPG in erythrocytes is reduced could cause a relative tissue hypoxia. However, measurements by ourselves

Table 1. *Respiratory, Hemodynamic, and Metabolic Values, Comparing Uneventful Surgical Convalescence With Noninfected Trauma and Sepsis*

	UNEVENTFUL CONVALESCENCE	POST TRAUMA (NO SEPSIS)		SEPSIS	
	Maximal Response	High Output (Post Shock)	Low Output (Hypovolemic Shock)	High Output (Maximal)	Low Output (Shock)
Respiratory					
$P_aO_2(F_IO_2 = 1.0)$ (mm Hg)	388 ± 44 (8)*	198 ± 50 (24)	221 ± 49 (6)	108 ± 38 (28)	106 ± 29 (16)
Shunt estimated (per cent)	12 ± 8% (6)	20 ± 8% (10)	14 ± 8% (6)	28 ± 7% (28)	34 ± 8% (16)
P_aCO_2 (mm Hg)	36 ± 6 (28)	32 ± 3 (30)	28 ± 6 (14)	30 ± 5 (32)	34 ± 5 (16)
Arterial blood pH	7.39 ± 0.03 (30)	7.43 ± 0.04 (22)	7.16 ± 0.11 (14)	7.47 ± 0.08 (32)	7.22 ± 0.11 (14)
Hemodynamic					
Cardiac index (L per M^2 per min)	3.6 ± 0.3 (30)	4.3 ± 1.0 (24)	1.7 ± 0.7 (12)	4.8 ± 1.6 (32)	1.9 ± 1.1 (16)
Central venous pressure (cm H_2O)	5 ± 3 (21)	10 ± 4 (21)	2 ± 3 (14)	12 ± 6 (32)	16 ± 6 (16)
Pulmonary arterial mean pressure (mm Hg)	18 ± 4 (6)	21 ± 5 (8)	14 ± 4 (6)	28 ± 5 (14)	29 ± 5 (13)
Left atrial (wedge) pressure (mm Hg)	8 ± 2 (5)	12 ± 5 (6)	7 ± 5 (6)	13 ± 5 (14)	15 ± 5 (13)
Mean arterial pressure (mm Hg)	87 ± 10 (30)	78 ± 14 (21)	57 ± 10 (14)	89 ± 12 (32)	62 ± 9 (16)
Metabolic					
Metabolic rate (kcal per M^2 per day)	980 ± 210 (16)	1131 ± 213 (7)	—	1240 ± 250 (18)	1040 ± 169 (12)
Body temperature (Tr °F)	100.7 ± 1.4 (30)	101.6 ± 1.6 (24)	97.5 ± 1.1 (14)	102.9 ± 1.7 (32)	99.1 ± 2.1 (16)

*Average values ± std. deviation (number of patients).

and others failed to disclose significant differences in p50 values of blood from septic or traumatized patients unless they have received many transfusions of stored blood.

Low Output Syndrome

Inability of the cardiovascular system to meet the elevated circulatory demand causes catecholamine secretion resulting first in venoconstriction and subsequently in arteriolar constriction. Many nonworking tissues, particularly skeletal muscle, are deprived of adequate perfusion. There are three principal causes for circulatory failure under these conditions:[11] (1) Reduced venous return caused by hypovolemia due to blood loss or secondarily to fluid translocation from the circulation into edema or other sites. Splanchic "pooling of blood," although common in dogs, does not appear to occur frequently in man. (2) Right heart failure secondary to elevated pulmonary vascular resistance is common. This phenomenon is demonstrated by the high central venous pressure associated with an elevated pulmonary artery mean pressure. High pulmonary vascular resistance is observed commonly in the septic patients. (3) Biventricular myocardial failure is demonstrated by the elevated left atrial (wedge) pressure observed in certain of the post-traumatic but more often in the septic patients. Reduction of myocardial contractility may play a significant role in the hypodynamic septic shock state. Cohn and Del Guercio,[13] Siegal,[46] and Shoemaker[45] have made important observations indicating that patients with high cardiac output have better ventricular function than those in the hypodynamic state. Dr. Hechtman in a previous paper of this symposium has demonstrated by construction of "Starling curves" the presence of failure of the left ventricle with a significant descending limb as the left atrial pressure rises above 15 mm of mercury.

Although any cardiac output insufficient to satisfy the high circulatory demand may result in shock, it is significant that those patients with low output following trauma or the onset of sepsis range from 30 to 90 per cent of normal.[42] The average cardiac index is approximately 1.7 in the former and 1.9 L per M^2 per min in the latter. The low body temperatures which accompany post-traumatic or septic shock are an indication of the inability of the body to maintain metabolic heat production sufficient to offset the ambient heat loss. Reduction of body temperature below normal is a serious prognostic sign, and patients who remain hypotensive for more than 24 hours have a mortality rate in excess of 70 per cent.[32, 52]

ENERGY METABOLISM

Fuel Utilization in Trauma and Infection

Cellular functions such as ion transport, maintenance of osmotic gradients, synthesis, and motion are dependent upon the conversion of energy derived from body fuel substrates to high energy phosphate bonds, the common medium of biological energy exchange. The production of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) in-

volves the transfer of approximately 7700 kilocalories per mole in the process of aerobic or anaerobic phosphorylation. Great quantities of energy are derived from the complete oxidation of three substrates: carbohydrate=4 Kcal per gm, protein=4 Kcal per gm, and fat=9 Kcal per gm. Oxygen is the hydrogen acceptor required for complete oxidation to carbon dioxide and water. In the absence of oxygen, energy metabolism is dependent upon the inefficient degradation of carbohydrate to lactate which produces but 2 molar equivalents of ATP in contrast to the 36 produced by complete oxidation in the tricarboxylic acid (Krebs) cycle. The process of energy conversion by phosphorylation is ultimately dependent upon the cytochrome system.

As indicated in Table 1, the relative energy requirements in health and disease differ. The basal metabolic rate at rest (BMR) of a normal 70 kg man is about 1800 Kcal per day. Following severe trauma or during widespread sepsis this value may range from 2200 to 2800 Kcal per day.[10, 28] Fever in part accounts for the elevated caloric requirement. However, Kinney and Roe[30] observed that in such patients the energy expenditure considerably exceeds that predicted by the Du Boise formula,[16] which states that the metabolic rate rises about 7 per cent for each degree Fahrenheit of body temperature elevation. Increased work or respiration, elevated metabolic rate, as well as possible uncoupling of phosphorylation may account for this apparent discrepancy. Much greater expenditures of energy are encountered in large burns in which evaporative heat loss occurs.

The pattern of endogenous fuel substrate utilization differs significantly between uncomplicated normal starvation and that observed in seriously sick patients following trauma or infection. The most obvious differences are protein wastage, a pseudodiabetic state, and anaerobic glycolysis with lactate production. All in great measure are attributable to three factors: (1) the extent to which endocrine secretion is altered, particularly insulin, glucagon, corticosteroids, and the catecholamines; (2) the state of the transport systems (respiration and circulation); and (3) the limitations imposed by abnormal circulating agents on cells in various tissues to utilize available substrates or to respond to endocrine or other stimuli.

Derived from clinical studies of surgical patients at the Boston City Hospital, the Deaconess Hospital in Boston, and the Rhode Island Hospital, the data in Table 2 are presented to illustrate the metabolic abnormalities. The availability of energy fuel substrates is determined by their blood levels, and their utilization by peripheral tissues is measured by the product of femoral arteriovenous differences and the estimated femoral blood flow. Normal fasting is compared with (1) uneventful surgical convalescence (moderate noninfected trauma), (2) the high cardiac output state of severe sepsis (the usual pattern of recovery from infection), and (3) the low flow state of sepsis (septic shock).

Normal Fasting

Six volunteer subjects fasted for 72 hours were studied by Dr. George Blackburn and his colleagues.[3, 4] *The noninfected trauma group*: con-

Table 2. *Peripheral Energy Metabolism in Man Comparison of Fasting, Noninfected Surgery, Sepsis, and Septic Shock*

ARTERIAL BLOOD CONCENTRATIONS OF SUBSTRATES AND METABOLITES

	FASTING 72 HOURS (N = 6)	CLEAN SURGERY (N = 7)	HIGH FLOW SEPSIS (N = 9)	LOW FLOW SEPSIS (SEPTIC SHOCK) (N = 9)
Blood insulin (μU per ml)	10 ± 8	30 ± 9	46 ± 4	6 ± 1
Glucose (mM per L)	3.7 ± 0.3	5.0 ± 0.6	8.3 ± .59	7.2 ± .71
Lactate (mM per L)	0.6 ± 0.04	0.8 ± 0.1	1.9 ± .20	3.14 ± .74
Glycerol (mM per L)	0.17 ± 0.05	0.13 ± 0.05	0.14 ± .01	0.10 ± .02
FFA (mM per L)	1.2 ± 0.04	0.84 ± 0.42	0.65 ± .12	0.96 ± .15
Ketone (mM per L)	2.0 ± 0.5	0.8 ± 0.02	0.014 ± .004	0.035 ± .007
Alanine (mM per L)	0.18 ± .02	0.28 ± .04	0.27 ± .03	0.434 ± .052

ESTIMATE OF PERIPHERAL UPTAKE OF SUBSTRATES AND RELEASE OF METABOLITES BY THE LEG

	UPTAKE OR RELEASE (μM per M^2 per min)	UPTAKE OR RELEASE (μM per M^2 per min)	UPTAKE OR RELEASE (μM per M^2 per min)	UPTAKE OR RELEASE (μM per M^2 per min)
Glucose	+0.19 ± .02	+0.22 ± .03	+0.21 ± .02	+0.33 ± .06
Lactate	−0.08 ± .02	−0.21 ± .04	−0.34 ± .02	−0.44 ± .12
Glycerol	−0.09 ± .01	−0.14 ± .03	−0.07 ± .02	−0.06 ± .02
FFA	+0.72 ± .20	+0.08 ± .02	+0.10 ± .03	+0.11 ± .04
Ketone	+0.11 ± .02	+0.07 ± .02	+0.0 ± .01	+0.0 ± .01
Alanine	−0.05 ± .02	−0.096 ± .03	−0.14 ± .02	−0.21 ± .07
N balance (gm per day)	−9 + 2	−14 ± 2	−16 ± 3	−18 ± 4

sisted of six patients who underwent uneventful convalescence following major surgery. The determinations were made 72 hours postoperatively, during which time each patient had received only saline infusions. *The high flow septic group*: consisted of patients with cardiac indices greater than 2.8 L per M^2 per min. They are similar to the high output septic group presented in Table 1. No patients with mild or well localized chronic sepsis were included. All had positive cultures for coliform and other enteric organisms in the blood or from the wound. No glucose was administered for 12 hours prior to the sampling period. Each was considered to be in a "semi-starved state." Those in the *low flow septic shock group* were septic patients who exhibited cardiac indices less than 2.8 L per M^2 per min and who gave other evidence of inadequate perfusion.

Hemodynamic measurements included cardiac output determined by thermal dilution, employing a Swan-Ganz catheter.[50] Although regional blood flow of the leg was measured by indocyanine green dye dilution curves in five instances, in the majority the cardiac index was employed

as an indirect measurement of regional blood flow. The validity of this derived value for regional limb flow was based upon direct measurements of leg flow provided by Finley et al.[19] and by our own observations in man and in animals.[12] Approximately one-fifth of the cardiac output goes to each leg in the resting state, being slightly greater proportionally (f=1.2) in the high output state. The estimate of uptake or release of substrates and metabolites may be arrived at by multiplying the arterial venous difference times estimated blood flow. These values are presented in the lower portion of Table 2, and are based upon flow in the leg relative to the surface area of each patient, making possible comparison between people of differing size.

Blood samples for determination of arterial-venous differences were obtained from the femoral vein and from the radial artery. Glucose, lactate, glycerol, and alanine were determined enzymatically by methods adapted from Bergmeyer,[2] FFA was measured by the method of Dole,[15] and radioimmunoassay according to the method of Soeldner[48] was employed for blood insulin concentration.

Normal Fasting

To appreciate the significance of the altered energy metabolism encountered after trauma or in the presence of sepsis, it is essential to understand the utilization and storage of body fuel in the normal fed and fasted states. The available stored energy in the body of the normal adult consists of small quantities of carbohydrate in the form of glycogen (about 200 gm), approximately 6 kg of protein, and on the average about 15 kg of fat. Available carbohydrate in normal starvation is exhausted in approximately 15 to 20 hours. Initially, as much as 75 gm of protein per day will be mobilized for conversion to carbohydrate, normally required by nervous tissue and blood cells.[6] The remainder of the caloric requirement is derived from fat. As the adaptation to starvation progresses the quantity of mobilized protein may be reduced to as little as 25 gm per day. This results in a negative nitrogen balance of approximately 4 gm. Proportionately more fat is utilized, as free fatty acids are mobilized by lipolysis. Approximately 20 per cent of the available free fatty acids are converted to ketones in the liver.[33] Progressively greater utilization of ketones by the nervous system takes place. The mechanism of this conversion to an economic utilization of fat stores is dependent upon a progressive reduction of circulating insulin. The normal overnight fasting value of blood insulin varies between 16 and 20 μU per ml. As fasting continues this value may decline below 12 μU per ml, as shown in the first column of Table 2. Cahill[7] has described insulin as the "overall fuel control in mammals." Insulin at a high level promotes glycogen, protein, and fat synthesis, at the same time suppressing lipolysis. In starvation, as blood glucose declines from an initial fasting value of approximately 7 μM per ml to less than half that value, insulin secretion decreases. Fat is mobilized to furnish an elevated level of FFA, glycerol, and ketones. FFA and ketone utilization by cells is proportional to their plasma concentration.[39] Within 72 hours in the fasting volunteers the FFA had risen to 1.2 mM per L and ketones to 2.0 mM per L. The measurements of arteriovenous difference

and blood flow in the leg indicate that the uptake of FFA was 0.72 μM per M^2 per min while ketones were used at a rate of 0.11 μM per M^2 per min. Alanine constitutes approximately 10 per cent of the amino acid structure of muscle protein. Because of transamination of pyruvate it represents between 40 and 50 per cent of the amino acids released from such muscle. Therefore, it is a good indicator of the extent to which protein degradation and oxidation of branch chain amino acids (BAA) in muscle is occurring.[18, 35] In this group of fasting volunteers the release of alanine amounted to but 0.05 μM per M^2 per min.

Noninfected Trauma of Clean Surgery

Comparing the findings in this group of patients, shown in the second column of Table 2, with those of fasting, it is evident that the glucose levels in the blood are higher. At the same time free fatty acids and ketones in the blood are significantly lower. The result is that the uptake of free fatty acids and ketones by the lower extremity are but one-tenth of that found in normal fasting. Lactate production is threefold that of the normal fasting state. Since glucose uptake remained essentially the same, it is apparent that approximately half the glucose uptake is being converted to lactate despite adequate oxygenation of the tissues by a relatively high blood flow. The resulting fuel deficit caused by the anaerobic degradation of glucose and the very much reduced uptake of FFA and ketones is compensated by a significant increase of amino acid oxidation locally. This is reflected by a doubling of alanine release and the greater negative nitrogen balance of 14 gm per day.

High Flow Sepsis

Despite high blood insulin levels which averaged 46 μU per ml, the arterial blood glucose of the hyperdynamic septic patients at 8.3 mM per L was more than double that of the fasting volunteers. In spite of the hyperinsulinemia the glucose uptake by the extremities was essentially the same, but lactate production was more than four times as great. The net result was that but one quarter of the glucose uptake was being fully oxidized. At the same time lipolysis was reduced as indicated by the small release of glycerol which amounted to only 0.07 μU per M^2 per min. Fat utilization was further limited and ketone uptake was almost nil. The release of alanine from the muscle was three times that of the fasting volunteers and was reflected by a negative nitrogen balance of 16 gm per day. Although the two glucogenic precursors lactate and alanine were both elevated above normal values they were both significantly less than that observed in the septic shock patients. This indicates that glucogenesis was active in the liver, the only route for clearing these substances from the blood. The average blood glucagon level was 546 ± 96 pg per ml.

Low Flow Septic Shock

The arterial glucose levels were high, the average value being 7.2 mM per L, as might be expected, with an insulin level reduced to 6 μU per ml. However, glucose uptake by the extremity was elevated to 0.33 μM per M^2

per min. Because of circulatory insufficiency and anaerobic conditions lactate production was more than five times that observed in the fasting and significantly greater than that observed in the high flow state.

Despite a relatively high blood FFA level, probably associated with elevated catecholamine secretion, there was a net release of fat from the limb as determined by a comparison of glycerol and FFA release (see Table 2). The arterial ketone body level was increased three fold over that of the high flow septic patients, but uptake by the limb was negligible. Because of the marked fuel deficit caused by lack of FFA and ketone utilization combined with marked conversion of glucose to lactate, the apparent fuel deficit was greater than in any of the other groups. Alanine release was four times that of the fasting volunteers and half again greater than the high flow septic state. This phenomenon was reflected in the highest observed negative nitrogen balance which averaged 18 gm per day. The presence of high levels of lactate (3.1 mM per L) and alanine (0.43 mM per L) indicates that liver clearance of these substances by glucogenesis was unable to keep pace with their production. If not corrected by a restoration of adequate circulation, the metabolic defect accompanied by progressive acidosis usually results in death within 24 to 36 hours.

INDUCTION OF INSULIN RESISTANCE

The diabetic type of glucose tolerance curve observed after trauma or the onset of infection despite a normal elevation of insulin in response to hyperglycemia has been recognized for some time.[25, 44] The failure of the limb in the patients studied to increase its glucose uptake in trauma and high flow sepsis despite the presence of hyperglycemia and hyperinsulinemia strongly supports the view that an insulin resistance exists in peripheral tissues. The experimental findings of Ryan et al.[43] of reduced glucose transport and activity of pyruvate dehydrogenase (PDH) in skeletal muscle of septic animals confirms this concept. PDH normally is induced by insulin. Increased lactic acid production may well be related to a deficiency of PDH which is rate limiting in the conversion of pyruvate to acetyl CoA. However, the suppression of lipolysis and the reduced blood levels of FFA indicate that adipose tissue still responds to hyperinsulinemia. Thus, it appears that the insulin resistance in the periphery is primarily limited to muscle. What then are the causes of insulin resistance in muscle? Steroids and catecholamines have been implicated. Although both are antagonists to insulin, neither has been demonstrated singly or in combination to produce this precise pattern. Therefore, the existence of another "active agent" in blood capable of altering metabolism in distant tissues has been postulated.

That such a substance or substances exist is suggested by recent experiments in our laboratories. Cannulation bilaterally of the femoral vessels in a pig for sampling and measurement of blood flow permit measurements of substrate uptake and metabolite production.[36] Slow infusion of 5 ml of normal human plasma into the artery of one leg

produces no change. However, infusion of 5 ml of plasma from a post-traumatic or septic patient causes within 30 minutes a doubling of flow rate and of lactate production while a modest reduction of glucose uptake occurs.

Similar results were obtained in the hindquarters of anesthetized rabbits. The aorta below the renal vessels was cannulated for sampling and to measure blood flow with the sine wave flowmeter. At the same level the inferior vena cava was cannulated for sampling. Whole plasma or fractions of plasma from normal and septic patients were infused slowly into the lower aorta. No changes in arterial blood pressure or plasma pH and Po_2 or concentrations of glucose, lactate, FFA, or amino acids were observed. In each instance blood insulin remained unchanged. Normal plasma or plasma fractions from normal persons were infused over a 15 minute period, no alterations of glucose uptake or lactate production were observed. However, a similar infusion of 3 ml of plasma from a seriously septic or traumatized patient produced 61 ± 10 per cent increase of blood flow. Lactate production rose 56 ± 16 per cent while glucose uptake declined 46 ± 13 per cent below the control. No significant differences in oxygen consumption or uptake of FFA took place. When the plasma was separated into fractions containing different molecular weights by cold pressure filtration through membranes of different pore sizes, that fraction which contained substances of molecular weights between 1000 and 10,000 from plasma septic patients produced a consistent reaction similar to that of plasma from such patients. These findings confirm the presence of a circulating substance of moderate molecular size in the post-traumatic and septic state which is capable of inducing an insulin resistance primarily in muscle tissue which is demonstrated by suppression of muscle glucose uptake and increase of lactate production.

A variety of substances suggest themselves as the "active agent" which may induce these metabolic abnormalities, particularly in muscle. Necrosis of tissue is caused locally both by trauma and invasive infection. Remote cellular injury accompanied by abnormal metabolism may result from bacteremia or from toxic products associated with cellular and bacterial destruction. Bacterial exotoxins capable of destroying tissue are characteristic of the gram-positive cocci and certain of the clostridia. Endotoxins, principally derived from gram-negative coliform organisms, are lipopolysaccharides embedded in the bacterial membrane structure and released only on dissolution of the bacterial cell. The injurious component is "lipid plasma A." Its structure consists of even numbered saturated and unsaturated fatty acids attached to the carbohydrate backbone by amine linkages. Cellular damage is caused by the ability of endotoxin to complex with the molecular structure of membranes.[27] Endotoxin per se has been shown to be capable of altering or blocking enzymatic pathways in liver and certain other tissues, particularly those involved in oxidative phosphorylation and ATP production.[34] However, the pattern of high blood glucose levels observed in the post-traumatic and septic patients is significantly different from that produced by endotoxemia in animals in which hypoglycemia due to failure of hepatic glucogenesis is usually observed.[37]

Tissue injury and cell death, principally of macrophages, results in the release of a variety of lysosomal enzymes, many of which are potent proteolytic peptidases. Hageman factor (Factor XII) is activated by peptidases or by the complexing of endotoxin, antibody, and complement, to initiate the clotting cascade and the production of disseminated intravascular coagulation. Thromboplastin from damaged tissue or injured vascular endothelium as well as the aggregation of platelets accentuates clotting. Simultaneous conversion by Hageman factor of plasminogen to plasmin may produce fibrinopeptides and other fibrin breakdown products. Platelet aggregation, frequently demonstrated by thrombocytopenia, is accompanied by platelet release of a variety of vasoactive substances including serotonin, ADP, and prostaglandins. The kinins, also potent powerful vasoactive substances, are activated by Factor XII. All of these agents alter capillary permeability and may have other membrane effects. Each of these are demonstrated to have a clear cut effect on the lung in the induction of interstitial pneumonitis.[11] However, the molecular weights of such substances make it improbable that any with the possible exception of certain fibrinopeptides are the active agent inducing the alteration of muscle metabolism. Many other proteins or peptides may be altered or denatured by proteases, any one of which may induce the observed metabolic changes. The important point is that such a substance or substances must exist, for the abnormal metabolism does not disappear until the gangrenous or septic focus is eliminated.

METABOLIC SIGNIFICANCE

The mobilization and utilization of endogenous fuel substrates after trauma or in the presence of severe infection differs significantly from the economic pattern of fat utilization and protein sparing observed in normal fasting and starvation. The cardiac output and the degree of tissue hypoxia add another dimension, as shown by the data obtained from patients in low output shock. The important point is that an energy fuel deficit, in muscle, whether caused by muscle insulin resistance in the hyperdynamic circulatory state or by tissue hypoxia in shock, has widespread repercussions to metabolism in all tissues. If prolonged, proteolysis in muscle leads to excessive hepatic glucogenesis, depletion of muscle protein and weakness. Reduction of protein synthesis with all that this implies to enzyme function and loss of immunocompetence are all part of this phenomenon. If not reversed by eliminating the stimulus of the septic or gangrenous focus or by adequate nutritional support of protein synthesis, death results.

Since Cuthbertson's original demonstration of a negative nitrogen balance,[14] it has been assumed that proteolysis occurs in order to furnish energy to satisfy the body's requirements for energy. The data presented here suggest a different interpretation. Muscle insulin resistance, regardless of cause, is rapidly induced after trauma or the onset of infection establishing the sequence of events which lead to a local energy fuel

deficit. Glucose transport is not increased despite hyperglycemia and hyperinsulinemia. The increased production of lactate even in the face of adequate or high blood flow and normal oxygen consumption[12] decreases the amount of glucose fully oxidized. Due to suppression of lipolysis, the availability of FFA and its uptake are significantly reduced. The production of ketones by beta oxidation in the liver is impaired, and the uptake of these important substrates by the limb decline nearly to zero. To satisfy the energy requirement of muscle it is forced to oxidize the branch chain aminoacids (leucine, isoleucine, and valine) derived from its own protein structure.

Alanine is produced by transfer of NH_3 from oxidized amino acids by transamination to pyruvate.[21] Alanine, lactate, and glycerol as well as certain other aminoacids are cleared from the blood by hepatic glucogenesis.[35, 38] Rocha et al.[41] and Unger et al.[51] have shown that the alpha cells of the pancreas probably are stimulated by alanine to secrete glucagon which in turn induces glucogenesis and ureagenesis in the liver. Experimentally in sepsis[26] and in a variety of clinical situations[35] it has been demonstrated that the rate of glucose release by the liver is proportional to the delivery of these glucogenic precursors to it. The glucose concentration in the blood increases, followed by a rise of insulin secretion from the pancreatic beta cells. The cycle is completed, and is reflected by the large negative nitrogen balances observed.

Explanation thus is offered for the demonstrated augmentation of the glucose pool in the body under these conditions.[22, 31] Also the inability to stop glucogenesis by the infusion of glucose is explained, since only by glucogenesis can lactate, alanine, and other glucogenic precursors be removed. It is apparent then that these alterations of peripheral metabolism are responsible for an increase of glucose rather than an energy demand by all tissues causing the abnormal proteolysis and oxidation of aminoacids.

The other important aspect of this phenomenon, failure of protein synthesis whether in the wound, by the liver, or in any other tissue, is due to the removal of the branch chain amino acids by oxidation. Protein is continually being degraded and resynthesized.[20] Unless all component essential amino acids in the structures of a given protein are present, protein synthesis by the endoplasmic reticulum cannot be completed. Drs. Ryan and Border in their articles both point out the mechanism and importance of this phenomenon in accounting for the progressive and often rapid decline of albumin and other secretory proteins observed in this type of starved injured or septic patient.

The low output shock state presents a somewhat different picture. The presence of high catecholamines enhance glucose transport, but the marked elevation of lactate production related to muscle tissue hypoxia increases the fuel deficit. Insulin secretion is suppressed by catecholamines in any form of shock.[8, 24] Lypolysis is no longer suppressed and FFA is available. However, ketone production by the liver almost ceases. The very severe fuel deficit remains and leads to an even greater degree of amino acid consumption in muscle. In this state are observed the greatest negative nitrogen balances.

SUMMARY AND CONCLUSIONS

Contrasting with normal starvation, the severe proteolysis and excessive gluconeogenesis typical of sepsis and trauma are in general proportional to the total injury inflicted upon tissues both locally and in distant organs throughout the body. Evidence from observations on the utilization of substrates by peripheral tissues strongly suggest the relationship of proteolysis and glucogenesis to the presence of an energy fuel deficit in skeletal muscle, whether established by an insulin resistance or by insufficient perfusion in shock.

In the presence of the high cardiac output, characteristic of the patient who will recover, muscle insulin resistance is indicated by the lack of increased glucose uptake by the leg despite hyperglycemia and elevated blood insulin. On the other hand, a reduction of blood free fatty acids suggests that adipose tissue continues to respond to insulin. To satisfy the resulting energy fuel deficit occasioned by increased lactate production and by reduced availability of both free fatty acid and ketones, branch chain amino acids (BAA) are oxidized in the muscles. Alanine is produced by transamination. Hepatic glucogenesis and ureagenesis are stimulated to clear from the blood the lactate, alanine, and other glucogenic precursors. In shock the metabolic defect is compounded by severely reduced insulin secretion and by tissue hypoxia.

Thus, the insulin resistance and energy fuel deficit in muscle makes available large quantities of glucose derived from muscle amino acids or lactate. From a long term point of view, the deficit in the amino acid pool thus created causes progressive failure of protein resynthesis or de novo synthesis in all organs. If unchecked, this defect may be fatal. Much can be done to support the patient by the correct use of alimentation whether by the gastrointestinal tract or parenterally. Because of the high rate of proteolysis during infection it is of importance to attack this problem early and continuously to avoid the serious consequences. Of course, the preferable route of alimentation is by the intestinal tract. If malfunction or fistulae preclude a full diet, excellent nutrition can be maintained at times by amino-acid containing elemental diets, provided that some absorptive capacity exists. Failing this parenteral alimentation, presented in detail by Dr. Blackburn in the final article of this symposium, must be employed to: (1) spare protein, and (2) furnish the requisite calories. These data make it evident that the branch chain amino acids are required in a greater proportion to replace those consumed by their peripheral utilization in muscle. In the low output shock hypoinsulinemic state, some success in restoring normal cardiac function and metabolism generally has been attained by the administration of large doses of insulin.[12]

Vital function of every cell, including enzyme activity, motion, and hundreds of others essential to survival, depend upon energy and synthesis. Not only are fuels required to satisfy this need but each organ is dependent upon the function of others to continue its own. Because of the far reaching detrimental effects of trauma and sepsis throughout the body, it is of the greatest importance to understand the physiologic responses including a high cardiac output, which characterize the pattern

of survival and recovery. In addition to correct alimentation treatment of failure in any system, circulatory, respiratory, renal, or other must be directed toward restoration of the physiologic pattern of recovery.

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Total Body Potassium and Nutritional Status

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The body cell mass was defined by Moore as that component of body composition "containing the oxygen-exchanging, potassium-rich, glucose-oxidizing, work-performing tissue."[5] The body cell mass is in effect the living component of body composition and therefore its measurement permits a quantitative assessment of the nutritional state of the individual. Unfortunately, the body cell mass cannot be measured directly. However, a linear relationship has been demonstrated between the body cell mass and total exchangeable potassium (K_e), which is equal to total body potassium.[8] Moore et al.[5] described an excellent correlation, with narrow confidence limits, between the intracellular water volume and K_e, in a large group of normal volunteers. Kinney et al.[3] demonstrated that the resting metabolic expenditure is a function of K_e. Talso et al.[6, 7], in a large group of patients with a variety of water and electrolyte abnormalities, reported a constant potassium to nitrogen ratio in skeletal muscle, despite marked variations in the muscle content of water, sodium, potassium, and nitrogen. Recently, by means of a whole body counter and neutron activation analysis, an excellent correlation was reported between the total body nitrogen and K_e in 164 patients.[2] There are thus considerable data in the literature supporting the use of K_e as an indirect measure of the body cell mass.

Isotope dilution with a radioactive isotope of potassium is the method of choice for measuring K_e. Unfortunately, the radioactive isotopes of potassium, which are commerically available, namely potassium-42 and potassium-43, decay rapidly with half lives of 12.5 and 22.4 hours respectively. Their use in clinical studies is therefore logistically inconvenient and expensive. The whole body counter offers an alternate method of measuring K_e. This method is based on the fact that 0.012 per cent of all naturally occurring potassium is in the form of potassium-40, which is radioactive. However, the whole body counter is an expensive installation. In addition its calibration remains a difficult problem.[9] A technique has therefore been developed which indirectly measures K_e. This method involves the use of sodium-22 and tritiated water. Both isotopes are safe and convenient to use in clinical investigaions.

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THE INDIRECT MEASUREMENT OF K_e

The indirect measurement of K_e was based on the hypothesis that the ratio (R), where

$$R = \frac{Na + K}{H_2O} \qquad (1)$$

where Na = sodium content
K = potassium content
H_2O = water content

is a constant for all tissues within any individual. This hypothesis was based on the absence of a significant osmotic gradient between the intracellular and extracellular compartments (except for several specialized tissues) and on the fact that the major source of osmotic pressure of total body water is the electrolytes, of which sodium and potassium are the two principal cations. If the ratio R is a constant for all the tissues within the individual, it follows that it must also be equal to the sum of all the tissues, i.e.,

$$R = \frac{Na_e + K_e}{TBW} \qquad (2)$$

where Na_e = total exchangeable sodium
TBW = total body water

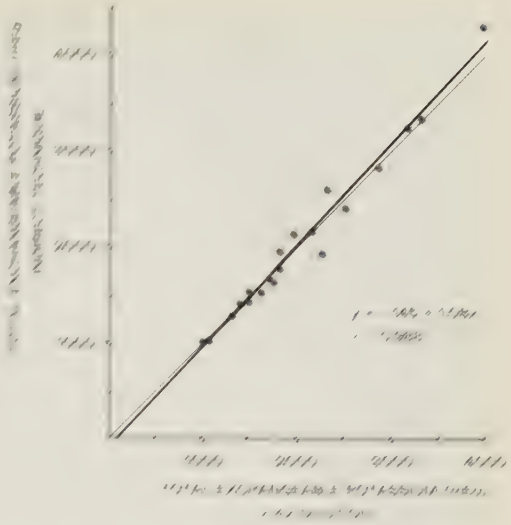
Rearranging equation 2 results in the following:

$$K_e = R\,(TBW) - Na_e \qquad (3)$$

The latter relationship indicates that K_e can be calculated if the remaining parameters are measured. TBW and Na_e can both be easily measured by isotope dilution using tritiated water and sodium-22 respectively. In addition, the ratio R can be determined by measuring the sodium, potassium, and water content of a sample of whole blood.

The validity of equation 3 has been demonstrated experimentally in both man and several laboratory animals.[10] The experiments involved both normal animals and animals with a variety of pathologic states. Because of space limitations only the results of the human studies will be summarized.

In 20 patients, many of whom were in a terminal state because of neoplastic disease, K_e was simultaneously determined indirectly and directly by potassium-42 dilution. The correlation between the two sets of measurements were excellent with a correlation coefficient of 0.99 (Fig. 1). In addition, in a group of 25 normal volunteers, where K_e was expressed as a function of TBW (K_e/TBW), to normalize for the variation in body size, the mean K_e/TBW was 80.0 (SEM = 1.03) mEq per L. The



lower and not significantly different from the mean of 21% (S.E.M. = 1.1%, ref. 9) as calculated from the data of Moore et al. [10] who measured K_e by K-42 dilution in 33 normal individuals.

The indirect determination of K_e involves the intravenous injection of 200 microcuries of tritiated water and 5 microcuries of sodium-22. A 10 ml whole blood sample is obtained at 24 hours. In addition, the urine excreted during this period is collected to determine the amount of isotope excreted during the 24 hour equilibration period. The TBW volume and Na_e are determined by mixing equal volumes of the 24 hour plasma sample and a 10 per cent trichloroacetic acid solution to precipitate the plasma proteins. One milliliter of the resultant supernatant is added to 15 ml of a liquid scintillation solution (Aquasol, New England Nuclear), and counted in a liquid scintillation counter. Differential counting is employed to determine the plasma concentration of each isotope. This involves counting each sample with two different window settings on the pulse height analyser. Each window corresponds to the major energy peak of the radiation given off by each isotope. The amount of isotope excreted during the 24 hour equilibration period is determined by measuring, in a similar manner, the concentration of the two isotopes in the urine. The TBW volume is given by

$$TBW = \frac{\text{counts/min injected} - \text{counts/min excreted}}{\text{plasma tritium concentration at 24 hours}}$$

and the Na_e is determined from

$$Na_e = \frac{(\text{counts/min injected} - \text{counts/min excreted})\,(\text{plasma Na conc.})}{\text{plasma Na-22 concentration at 24 hours}}$$

To determine the ratio R, a 1 ml aliquot of the 24-hour whole blood sample is desiccated to constant weight to obtain the water content. The whole blood sodium and potassium concentrations are determined by flame photometry and corrected for water content. The ratio R is calculated using equation 1. With the direct measurement of Na_e, TBW, and the ratio R, it is possible to calculate K_e using equation 3.

The indirect measurement of K_e, described above, is accurate, safe, and simple to perform. The isotopes employed are inexpensive and relatively stable. The half-life of tritium and sodium-22 is 12.4 and 2.6 years respectively. The total radiation exposure to patients resulting from the intravenous injection of these isotopes is 257 mRem, which is much less than the radiation received from either a barium meal or an intravenous pyelogram. In addition, both TBW and Na_e are important body composition parameters. The TBW is important as it serves as the independent variable, i.e., it is used to correct for variation in body size. Moore et al.[5] have demonstrated that the various parameters of body composition correlate better with TBW than body weight. Thus, when normalizing for body size, both K_e and Na_e can either be plotted against the TBW volume or expressed as a function of TBW, i.e., Na_e/TBW and K_e/TBW (Fig. 2).

Na_e is also an important body composition parameter as it is a measure of the extracellular supporting component of body composition. With malnutrition, as the body cell mass contracts, indicated by a decrease in K_e, Na_e increases, i.e., the extracellular component of body composition expands. Thus the ratio of Na_e to K_e (Na_e/K_e) becomes a sensitive index of the state of nutrition.

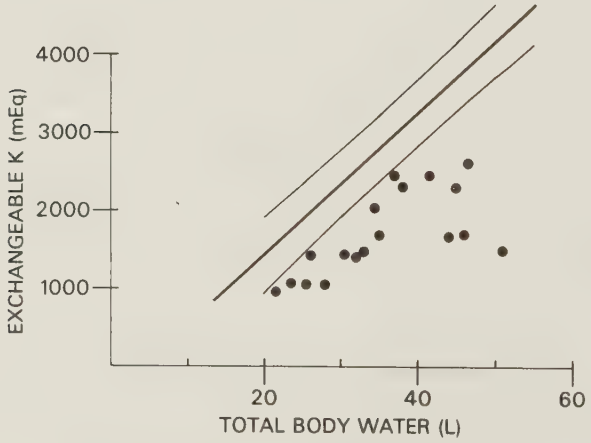


Figure 2. The K_e is plotted as a function of TBW for 18 patients who are in a chronic catabolic state. Included are the regression line and 95 per cent confidence limits determined from the data obtained in 25 normal volunteers. The normal range is therefore defined by the area bounded by the two outer confidence limits.

CHRONIC CATABOLIC STATE

The measurements described above were performed in 18 patients who were in a chronic catabolic state. The majority of these patients were in our surgical intensive care unit for a prolonged period of time with a variety of problems (sepsis, gastrointestinal fistulae, pancreatitis, inflammatory bowel disease, etc.). Intravenous hyperalimentation was indicated in all of these patients, but was not administered for a variety of reasons. The normal range of Na_e and K_e was defined by similar measurements in a group of 25 normal volunteers (see Fig. 2). In both the normal and catabolic patients the data were normalized for variation in body size by expressing Na_e and K_e as a function of TBW (Fig. 3). As expected the body cell mass was markedly contracted in the catabolic patients as indicated by a K_e/TBW of 49.2 (SEM = 2.3) mEq per L. This was significantly lower ($p < .05$) than the mean of 80.0 (SEM = 1.0) mEq per L observed in the normal volunteers. In contrast, the extracellular component of body composition was expanded in the catabolic group as indicated by a mean Na_e/TBW of 96.9 (SEM = 4.8) mEq per L, compared to a mean, in the normal group, of 77.5 (SEM = 0.9) mEq per L. Because in the catabolic patients the Na_e increased while the k_e decreased, the ratio Na_e/K_e was a sensitive index of the individual's state of nutrition. The latter ratio is in effect a measure of the extracellular component of body composition, expressed as a function of the body cell mass. In the normal group the mean ratio was 0.98 (SEM = 0.2), compared to 2.1 (SEM = 0.14) in the catabolic group.

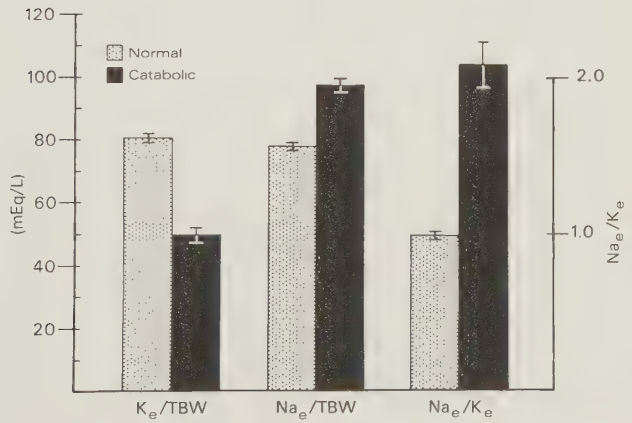


Figure 3. The mean and standard error of the mean for the data obtained from the 25 normal volunteers and the 18 patients who were in a chronic catabolic state. The K_e/TBW is a measure of the body cell mass while the Na_e/TBW is a measure of the extracellular supporting component of body composition.

THE PROTEIN SPARING EFFECT OF AMINO ACID SOLUTIONS FOLLOWING MAJOR SURGERY

Following a major surgical procedure the normal patient experiences a short but intensive period of catabolism, which is directly related to the severity of surgical trauma.[4] In most instances this catabolic state persists for 2 to 5 days and is characterized by positive water and sodium balance, and negative nitrogen and potassium balance.

Recently Blackburn and Flatt[1] proposed the hypothesis that significant protein sparing can be achieved by avoiding the intravenous infusion of glucose containing solutions in the postoperative period and using an amino-acid solution to infuse the required fluids and electrolytes. This hypothesis is based on the inhibition of fat mobilization by the rise in plasma insulin secondary to the intravenous infusion of glucose. The decreased availability of lipid, as an endogenous fuel, in the semistarved patients, necessitates increased protein breakdown to provide endogenous calories. The total calories infused intravenously, in the majority of postoperative patients, is insufficient to meet their daily requirements. In contrast, the infusion of amino acid containing solutions does not increase the plasma insulin concentration, permitting lipid mobilization to meet the daily energy requirements. In addition, the infusion of amino acid solutions supplies the daily protein requirement. Thus, according to this hypothesis, body protein is spared.

To test this hypothesis, the measurements described above were performed preoperatively and on the fifth postoperative day, in two groups of 19 patients each who were undergoing major abdominal surgery.[11] In the majority either a gastric or colon resection was performed. The patients were divided into the two groups depending on the type of fluid infused postoperatively. The first group received all their intravenous fluids and electrolytes as a 5 per cent glucose solution. In the second group, glucose containing solutions were excluded, and were replaced by a 5 per cent casein hydrolysate (Amigen, Baxter Laboratories).

In the patients receiving glucose, there was a significant ($p < .001$) decrease in the mean body weight of 2.6 kg on the fifth postoperative day while the TBW volume decreased by 0.58 liters. Since the lean body mass is equal to TBW/0.73 and body fat is the difference between the body weight and lean body mass,[5] the observed postoperative decrease in body weight was due to a decrease in both the lean body mass and body fat. In addition, in these patients there was a significant decrease ($p < .001$) in K_e of 391 mEq, indicating a loss of body cell mass. This was accompanied by an increase in the Na_e ($p < .01$), i.e., an expansion of the extracellular component of body composition.

In the group of patients receiving amino acids postoperatively, the mean body weight decreased by 2.0 kg ($p < .001$) by the fifth postoperative day. The mean TBW, on the other hand, increased by 1.3 liters ($p < .05$), implying an increase in the lean body mass. Thus the postoperative decrease of body weight in the patients receiving amino acid was due only to a loss of body fat. In contrast, as described above, in the glucose

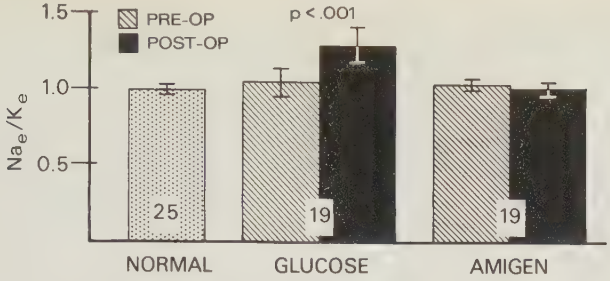


Figure 4. The mean and standard error of the mean of the Na_e/K_e ratio obtained in 25 normal volunteers, and in two groups of 19 patients each, both before and on the fifth day following a major abdominal operation. The required fluid and electrolytes were infused as a 5 per cent glucose solution in one group, and as a 5 per cent casein hydrolysate (Amigen) in the second group.

group the postoperative weight loss arose from a decrease of both body fat and lean body mass. In addition there was a small but statistically insignificant increase in K_e and a decrease in Na_e postoperatively, indicative of insignificant changes in the acqueous, that is non-fatty, component of body composition.

In this study the ratio Na_e/K_e was again a sensitive indicator of the state of nutrition. The mean ratio, preoperatively, was 1.04 (SEM = 0.8) and 1.03 (SEM = 0.4) in the glucose and Amigen groups respectively, which was not significantly different from the mean of 0.98 (SEM = .02) observed in 25 normal volunteers (Fig. 4). Postoperatively this ratio was unchanged at 1.00 (SEM = .03) in the Amigen group but had increased in the glucose group to 1.29 (SEM = 0.11), which was significantly ($p < .05$) different from the four other groups in Figure 4 by an analysis of variance and Scheffe's test. These data therefore support the hypothesis, first proposed by Blackburn and Flatt, that the infusion of amino acid solutions and the avoidance of intravenous glucose significantly preserves the body cell mass following a major surgical procedure.

THE EFFECT OF TOTAL PARENTERAL NUTRITION

For the normal patient undergoing elective uncomplicated surgery of moderate severity, a short catabolic period accompanied by semistarvation, although important, is not a critical factor in his ultimate recovery. However, this is not the case for the elderly with a compromised reserve, or the severely injured, or the patient with serious life-threatening complication such as sepsis, prolonged starvation, gastrointestinal fistulae, etc. In these patients, the amount and type of calories infused may be critical to their survival. Unlike starvation in normal man, these patients continue to utilize both fat and significant amounts of protein as endogenous fuel. Since there are no true stores of body protein, this continued protein catabolism results in a contraction of the body cell mass. Therefore the administration of intravenous hyperalimentation to patients who are in a chronic catabolic state is intended principally to preserve the body cell mass.

The simultaneous measurement of K_e, Na_e, and TBW thus provides an excellent means of quantitatively assessing the efficacy of total parenteral nutrition. These measurements were performed in three groups of patients receiving intravenous hyperalimentation. The first group of 18 patients received a solution containing 25 per cent glucose with 2.5 per cent crystalline L-amino acids for a mean of 14.5 (SEM = 1.2) days. Ten patients received a 25 per cent glucose solution containing 5 per cent casein hydrolysate for a mean of 19 (SEM = 3.0) days. In the third group of 7 patients, equal volumes of a 10 per cent Intralipid solution and a 7 per cent crystalline L-amino acid with 10 per cent fructose solutions were infused simultaneously for a mean of 11.6 (SEM = 1.8) days. The efficacy of this form of therapy was determined by measuring the K_e before and after a period of total parenteral nutrition. The patients studied were critically ill and chronically stressed surgical patients with a variety of complications. At this stage in the study, the number of patients in each group is too small to permit a comparison of the relative efficiency of the different solutions. However, the data do indicate a statistically significant relationship between the average total number of cal per kg per day infused and the mean daily change in K_e (Fig. 5). The correlation coefficient (r), which is statistically significant ($p < .001$), is only 0.5 because of the large scatter in the data. The scatter arises because the change in K_e is a small difference between two large numbers. Although K_e can be measured with an experimental error of approximately 5 per cent, the per cent error of the difference between two determinations increases as this difference becomes smaller. However, because the experimental error is random and not systematic, this problem is overcome by increasing the sample size.

The intercept of the regression line describing the correlation between the mean daily change in K_e and the calories infused was 51.3 cal per kg per day. Similar results were obtained when the daily change in the ratio of Na_e/K_e was plotted against the average caloric intake. As pointed out above, this ratio is a sensitive index of the state of nutrition. In this group of 35 patients the mean ratio prior to the commencement

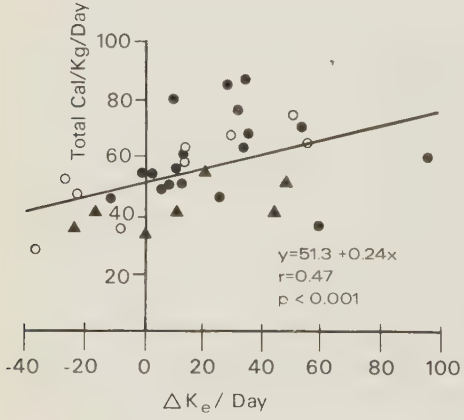


Figure 5. The mean total calories/kg infused per day was plotted against the mean daily change K_e in patients receiving three different solutions of intravenous hyperalimentation—as indicated by the closed circles (25 per cent glucose with 2.5 per cent crystalline L-amino acids), open circles (25 per cent glucose with 5 per cent casein hydrolysate), and triangles (equal volumes of a 10 per cent Intralipid solution and 7 per cent crystalline L-amino acid and 10 per cent fructose solution). The correlation between the two parameters was statistically significant.

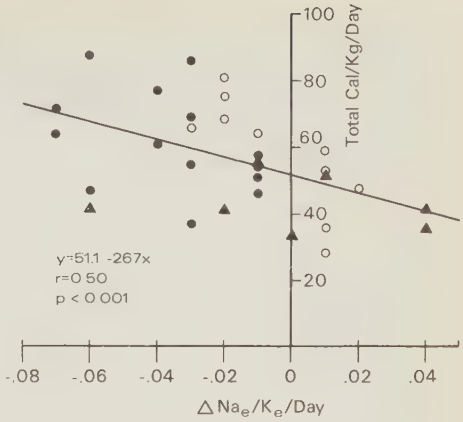


Figure 6. The same as Figure 5 except that the total cal/kg infused per day was plotted against the mean daily change in the Na_e/K_e ratio.

of intravenous hyperalimentation was 1.54 (SEM = .08). Thus any improvement in nutritional status results in a decrease in this ratio. Thus the inverse relationship observed between the daily mean change of Na_e/K_e and the total calories infused (Fig. 6). Because of the large scatter in the data, the correlation coefficient was only 0.50. Nevertheless, it was statistically significant ($p < .001$). The intercept of the regression curve was 51.1 cal per kg per day. Thus the data indicate that in this group of patients, nutritional balance was achieved by infusing approximately 50 cal per kg per day (see Figs. 5 and 6). The infusion of calories in excess of this amount should therefore result in an expansion of the body cell mass, while the opposite should occur when less calories are infused.

SUMMARY

A method for the indirect measurement of K_e is described. It is accurate, safe, and simple to perform in the clinical setting, and provides quantitative information regarding both the extracellular supporting component of body composition and the body cell. As a result, this technique was applied to quantitatively assess the nutritional status of several groups of surgical patients.

A marked contraction of the body cell mass, as indicated by a significant decrease in K_e, was recorded in a group of patients in a chronic catabolic state. The decrease in K_e was accompanied by a reciprocal expansion of the extracellular supporting component of body composition. Thus, in these patients, there was a large increase in the Na_e/K_e ratio. Similar changes, which however were much smaller in magnitude, were also observed following a major abdominal operation in a group of patients whose postoperative intravenous fluids contained glucose. In contrast, in a second similar group of patients, the above changes in Na_e/K_e were avoided, and postoperative protein sparing was achieved, by avoiding intravenous glucose in the postoperative period and infusing

instead solutions containing amino acids. Finally, data were presented which indicates that the effect of a chronic catabolic state on both Na_e and K_e can be prevented by administering intravenous hyperalimentation, provided that the total calories infused exceeded 50 cal per kg per day.

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Nutritional Care of the Injured and/or Septic Patient

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The practical results from extensive study of the metabolism of injury are the development of methods, technology, and products to support nutritionally every malnourished injured or septic patient.[24, 60] Recent developments in enteral and parenteral feedings rank with the discovery of antibiotics, heart/lung bypass, or renal dialysis, as major medical advances that can have a substantial influence on the survival of many patients who would otherwise not recover. However, the failure to recognize that the proper use of nutritional therapy has become a sophisticated science precludes satisfactory results in many patients.[66] Practitioners intending to use nutrition as a therapeutic modality must have proper training and practice it daily if complications are to be avoided and optimal care provided.[12]

Rarely does the clinician see a nutritional deficiency of significant clinical impact that is not also associated with protein-calorie malnutrition (PCM).[8] Although a favorable outcome may result in the care of many injured and/or septic patients, without developing a specific nutritional support strategy, this is a specious goal because it ignores the importance of protein and calories in the metabolic response to injury. Rather, the provision of fluid and electrolytes, the treatment of hypovolemia and acid base imbalance, and the provision of minerals and vitamins, along with protein and calories, are nutritional considerations. It is important not to limit the role of a nutritional support service to the latter nutrients but to see nutritional support as the major dependent variable to influence the metabolic response to injury.

Since protein and calorie support are the most difficult daily requirements to meet and since their utilization is uniquely interdependent,[55, 63] this review will concentrate primarily on their role in the development of a

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comprehensive nutritional support plan. Guidelines for fluid and electrolyte therapy[59] have been discussed elsewhere in this symposium and vitamin and mineral replacement can be provided easily (see Tables 7 and 8). Deficiencies in protein and calories are more slowly corrected and with more difficulty because of the "catabolic" hormones present during injury,[17, 38] the limited turnover of body protein that occurs each day,[26] and the large amounts of those nutrients required. This makes the restoration of body protein particularly difficult, and requires sophisticated techniques.

Among the major variables to be considered in the formation of a nutritional support plan are the body surface area, whether a child or an adult, the degree of nutritional depletion, degree of hypermetabolism, presence of secondary organ failure, and/or sepsis, and the primary disease process.[15, 17, 22]

Before discussing those key components of nutritional therapy, the metabolic response to injury will be briefly reviewed, followed by a discussion of the total amounts of protein and calories necessary and the ideal ratios of these nutrients in light of the metabolic consideration. Next, we survey the products that are presently available for treatment and in a fourth section deal with various nutritional states that would be desirable goals, with the description of the therapies used to achieve them. Finally, we consider the different clinical conditions, including nutritional status and organ failure, that will influence the nutritional support plan.

It should be realized that consideration of nutritional support during injury has been the subject of numerous books, workshops, and symposia in recent years. It is not the purpose of this review to reiterate this encyclopedia of knowledge. Most of the key references have been included in the references and the serious student is referred to these sources together with the American College of Surgeons' recent publication on surgical nutrition.[4] Also, we have developed these concepts in more detail elsewhere.[9–12, 14, 18]

THE METABOLIC RESPONSE TO INJURY

Trauma, sepsis, and injury have long been recognized as producing significant alterations in body metabolism.[23] This response—initiated by the central nervous system—is sympathetically mediated and triggers the release of substrate-mobilizing hormones (Fig. 1).[15, 67] During this initial or "acute phase," a generous mobilization of the metabolic reserves occurs, including skeletal protein which insures an adequate supply of substrates for energy production and biosynthesis, wherever they may be needed. The acute phase is followed by an adaptive phase during which the metabolism has adjusted to the different composition of nutrients available. This phase is characterized chiefly by elevated ketone levels, reduced glucose levels, and less nitrogen excretion.

The stress of illness effects a glucocorticoid-induced catabolism of peripheral protein resulting in an overall negative nitrogen balance

	"Ebb Phase"	"Flow Phase"		
	*	"Acute Phase"	"Adaptive Phase"	→ Convalescence
DOMINANT FACTORS:	Inadequate circulation	Catecholamines	Glucocorticoid	
SYMPTOMS:	Hyperglycemia Hyperlactic Hyperacidemia	Hyperglycemia Low insulin	Hyperglycemia High insulin	

When compared to equivalent *Food Deprivation WITHOUT Trauma:*

Fat Mobilization is:	Activated	Curtailed
Nitrogen Losses:	May be less!	Increased

Figure 1. The phases of normal response to trauma can be divided into the classic "ebb" and "flow" phase which gave characteristic hormonal and substrate responses. These metabolic consequences have important effects on the type and amount of nutritional support possible and desirable during injury.

which has classically been deplored.[49] Only recently have we realized that this peripheral catabolism might provide amino acids for the synthesis of acutely needed blood proteins, structural proteins, and enzymes.[15, 26] The recognition that the mobilization of body protein from skeletal muscle has purposes other than simply to provide precursors for gluconeogenesis is essential and must be considered when nutritional support therapies are designed.[17] This response is quite different from starvation without injury in which initial losses are from the liver and other labile visceral protein; it is only after 3 or 4 days of starvation that substantial mobilization of skeletal protein begins to take place.[64]

The hormones released during the acute catabolic phase of the response to injury specifically antagonize the action of insulin, the key anabolic hormone for the two major peripheral tissues: skeletal muscle and adipose tissue.[53] Glucocorticoids reduce the sensitivity of peripheral tissues to insulin while catecholamines inhibit its release.[53] The preservation of body cell mass appears to be temporarily sacrificed during the acute phase in favor of maintaining a relative abundance of circulating substrates to meet the requirements of any particular cell.

During the acute phase of injury the major energy reserve in the body—triglycerides stored in adipose tissue—are mobilized, making it possible to meet energy demands, even in severely caloric-restricted states.[29] This tissue contains some 3,500 calories per pound because of the high caloric value of fat and the low water content of the cells. For this reason it is clear that the concern about the lack of energy fuel substrate during the immediate postoperative period[52] or during conditions of starvation does not appear to be warranted.[21]

The acute phase of illness gives way to an adaptive phase during which the organism seeks to adapt its metabolism to the changes in the nature and source of nutrition. The timing of the transition between phases is dependent upon the degree of illness, injury or sepsis, and associated nutritional depletion.[15, 17]

Effective nutritional support can occur in this adaptive phase because the strong catabolic signals resulting from the high levels of catecholamines and glucocorticoids have subsided. The hormonal situation is complex, but the adaptive phase is recognized by the falling blood glucose, normal blood urea nitrogen, ketosis, ketonuria, and decreasing excretion of urea nitrogen. A fall in the blood glucose is of major significance in identifying this transition since it is well recognized that a high catabolic rate is associated with increased rates of gluconeogenesis and hyperglycemia.[45] It should be stressed that the administration of exogenous glucose, such as the infusion of 5 per cent dextrose solutions, prevents the identification of this transition and furthermore does not conserve the body's protein during the acute phase of injury.[17]

It is important to appreciate this timing when designing a nutritional support plan. The unnecessary intake of protein for metabolism to glucose via gluconeogenesis and ureagenesis or the unnecessary intake of calories for lipogenesis should be considered detrimental.[5, 47] Furthermore, work is expended on these processes and results in hypermetabolism.[12]

Optimal nutritional support equates with the retention of administered protein—net protein utilization—dependent upon a favorable hormonal environment. When these conditions are met, restoration of the body cell mass, particularly the visceral compartment, is the major goal of nutritional support.[14, 17] Maintenance of adequate protein synthesis will support the body cell mass ensuring a favorable organ response to injury.[8, 44]

The proper utilization of protein depends upon the availability of fuel substrates to meet the caloric requirements of synthesis. Otherwise, amino acids will be oxidized for energy via the gluconeogenic pathway.[44] The factors that will determine nitrogen balance and net protein utilization are the metabolic rate, nonprotein calorie intake, nitrogen intake, and the metabolic state in the terms described above.[55]

Special conditions exist during prolonged stress such as those observed in patients with major burns or systemic infection.[67] Nutritional support in these states is effective only in preserving the protein nutritional status.[19] Restoration must await the subsidence of hypercatabolism with the effective treatment of the disease. However, the use of standard parenteral hyperalimentation—hypertonic glucose with amino acids—can provide hemodynamic support by the inotropic effect of glucose, potassium, and insulin (GKI).[11, 65]

Thus one can see that a knowledge of the metabolic response to illness is necessary for the development of effective nutritional support plans; the phase of the response to injury, the extent of nutritional depletion, and the degree of hypercatabolism will influence the timing of therapy and patient benefits.

DEVELOPMENT OF A NUTRITION PLAN

A large group of protein and nonprotein calorie sources exists (Tables 1–3). These products allow the nutritionist a versatile armamentarium to meet the various demands that various organ system failures and disease states will present. Despite the potential complexity arising in patient care, nutritional support can easily be reduced to an effective plan by considering the following:

I. Nutritional assessment[12]
   A. Degree of depletion of lean body mass
   B. Visceral function
   C. Fat stores
II. Degree of hypercatabolism[55]
   A. Disease categories and measured or estimated metabolic rates
   B. Inspection of the patient, presence of tachycardia
   C. Rate of weight loss and nitrogen excretion (urea nitrogen) (see Table 4)
III. Gastrointestinal function
   A. History of dietary intake: adequate, insufficient, absent
   B. High or low fistula output
   C. Use of a nasogastric, transpharyngeal, gastric, enteric, or transfistula feeding tube.
IV. Appetite
   A. Solid or liquid food preference
   B. Taste preference—bland, fruits, sweet food groups
V. Goal of nutritional support
   A. Fed
   B. Non-fed
   C. Combination
VI. Route of nutritional support
   A. Enteral
   B. Parenteral
   C. Combination
VII. Protein and calorie requirements
   A. Basal Energy Expenditure (BEE) according to Harris-Benedict Standards[55]
   B. Protein at 1:150 nitrogen/calorie ratio

RATES AND RATIOS OF NUTRITIONAL PRODUCTS

The total intake and composition of nutrients is important if the body is to effectively synthesize protein. The daily calorie intake will depend primarily upon the patient's metabolic rate which, though difficult to measure clinically, can be estimated using the Harris-Benedict equations.[55] Calculation of the basal energy expenditure (BEE) takes into account age, height, weight, and sex rather than weight alone (kcal per kg). By regression analysis the delivery of calories in parenteral feeding at a rate of 1.76 × BEE/24 hours produces positive nitrogen balance with 95 per cent confidence in surgical patients who are mild to moderately catabolic.[55] Oral intakes of 1.54 × BEE/24 hours provide positive nitrogen balance with the same confidence limits in similar patients. This difference in caloric efficiency is primarily related to the constant infusion of hypertonic glucose and the lipogenesis that occurs secondary to the resulting hyperinsulinism.[12]

Text continued on page 1206

Table 1. *Composition and Indications for Use of Nutritional Supplements**

SUPPLEMENTS	CAL PER ML	MOSM PER L	PER CENT CAL PROTEIN	PER CENT CAL CARBOHYDRATE	PER CENT CAL FAT	N:CAL	PROTEIN SOURCE	CARBOHYDRATE SOURCE	FAT SOURCE	MEQ NA^+ PER L	FUNCTION
Citrotein	0.53		24.1	73.2	2.3	1:93	Egg white solids	Sucrose, dextrin-maltose	Mono- and diglycerides	23	Contains 50 per cent RDA of protein, vitamins, and minerals
Lanolac	0.66		21	30	49	1:81	Casein	Lactose	Coconut oil	1.1	Protein supplement for low sodium diets
Meritene (liquid), vanilla and chocolate	1.0	640	24	46	30	1:79	Skim milk Casein	Sucrose Lactose Corn syrup solids	Vegetable oil	40.5	Protein supplement
Sustacal (liquid), vanilla and chocolate	1.0	638 616	24	41.3	20.7	1:79	Skim milk	Sucrose Lactose Corn syrup solids	Partially hydrogenated soy oil	47.1	Protein supplement Low lactose content
Meritene (powder + skim milk)	1.0		35.9	62.4	1.7	1:43	Skim milk	Lactose Corn syrup solids	Cow milk fat	39.1	Protein supplement utilizing skim milk
Meritene (powder + whole milk)	1.0		26.4	44.8	28.8	1:48	Milk	Lactose Corn syrup solids	Cow milk fat	39.1	Protein supplement utilizing whole milk

Sustagen powder (normal dilution), vanilla and chocolate	1.8	721	24	68	8	1:79	Nonfat dry milk Powdered whole milk	Glucose Lactose Corn syrup solids	Cow milk fat	54.3	Protein supplement
MEAL REPLACEMENTS											
Compleat-B	1.0	468	16	48	36	1:131	Skim milk Beef	Lactose Sucrose	Corn oil Beef fat	59	Tube feeding: unflavored blenderized house diet for anabolism
Ensure: vanilla, banana, black walnut	1.06	460	14	54.5	31.5	1:155	Casein Soy protein isolate	Sucrose Corn syrup solids	Corn oil	32	Tube or oral feeding Lactose-free for anabolism
Isocal	1.05	350	12.9	49.6	38.5	1:169	Soy protein isolate Casein	Glucose Corn syrup solids	MCT soy oil	22.6	Tube feeding—unflavored Isotonic for anabolism
Nutri-1000	1.06	400	13	40	47	1:167	Skim milk	Glucose Sucrose Lactose Dextrin-maltose	Corn oil	23	Tube or oral feeding for anabolism
Portagen	1.0	354	16	44	40	1:160	Casein	Sucrose Corn syrup solids	MCT Safflower oil	27	Oral feeding for malabsorption of long chain fats and for anabolism

*Tables 1–3 and 5–9 reproduced by permission of Nutritional Support Services, New England Deaconess Hospital, Boston, Massachusetts.

Table 2. *Composition and Indications for Use of Defined Formula Diets*

DEFINED FORMULA DIETS	CAL PER ML	MOSM PER L	PER CENT CAL PROTEIN	PER CENT CAL CARBOHYDRATES	PER CENT CAL FAT	PER CENT CAL LINOLEIC ACID	N:CAL	PROTEIN SOURCE	CARBOHYDRATE SOURCE	FAT SOURCE	meq NA^+ PER L	FUNCTION (all DFD's are low residue clear liquid diets)
FOR MAINTENANCE												
Flexical Orange Vanilla Banana Fruit punch	1.0	805	8.8	61.1	30.1	2.16	1:264	Hydrolyzed protein + Methionine Tyrosine Tryptophan	Sucrose Lactose Dextrooligosaccharides	MCT Partially hydrogenated soy oil	15.2	30 per cent cal from fat 60 per cent cal from carbohydrate Protein source requires some digestion
Jejunal Beef broth Beverage Cherry Pudding	.91	990 1200	9.1	90.0	.82	.56	1:252	Crystalline amino acids	Glucose Dextrins	Safflower oil	33.7	60:40 essential to nonessential amino acid Easily absorbed protein source of high biologic value
Precision L-R Cherry Lemon Lime Orange	1.08	600	8.8	90.8	.65	.48	1:258	Egg albumin	Maltose Dextrins	Safflower oil	27.4	Low osmolality Protein source requires some digestion
Vivonex Vanilla Beef broth	1.0	610 678	8.1	90.3	1.3	1.04	1:286	Crystalline amino acids	Maltose Dextrins	Safflower oil	37.3	High osmolality when flavored

Orange		610										Easily absorbed protein source of high biologic value
Grape		610										
Tomato		610										
Chocolate		630										
Low Residue												
Beef bouillon	0.98	649	8.6	90.7	0.7	0.56	1:304	Crystalline amino acids	Dextrins	Safflower oil	68.8	Easily absorbed protein source of high biologic value
FOR ANABOLISM												
Precision-HN	1.0	580	16.6	82.9	0.42	0.33	1:125	Egg albumin	Maltose Dextrins	Safflower oil	40.5	Low osmolality Protein source requires some digestions
Citrus fruit												
Vivonex-HN	1.0		16.6	84.1	0.78	0.62	1:127	Crystalline amino acids	Glucose Maltose	Safflower oil	27.4	Easily absorbed protein source
Beef broth		920										
Orange		850										
Grape		850										
Strawberry		850										
SPECIAL DFD												
Aminade	1.02	1050	4	68	28	11	1:418	Essential amino acids	Sucrose Dextrins	Soybean oil	2	Provides high calorie, low protein diet of high biologic value (only essential amino acids) for use as Giordano-Giovanetti diet in renal failure Contains no vitamins

Table 3. *Feeding Modules for Enteral Alimentation*

FEEDING MODULES	CAL PER ML	PER CENT CAL PROTEIN	PER CENT CAL CARBO-HYDRATE	PER CENT CAL FAT	PROTEIN SOURCE	CARBO-HYDRATE SOURCE	FAT SOURCE	mEq NA^+ PER L	FUNCTION
CARBOHYDRATE									
Cal Powder	2.28					Glucose		5.6	Concentrated carbo-hydrate source
Hy-Cal	2.3	5.2	86.9	7.8		Glucose		5.9	Concentrated carbo-hydrate source Low electrolyte
Controlyte (powder)	5.0 per gm	Traces	72	24	Amino acids	Hydrolyzed cornstarch	Vegetable oil	0.43 per 100 gm	Concentrated carbo-hydrate source Low electrolyte
Polycose (powder)	4.0 per gm					Hydrolyzed cornstarch		5.3 per 100 gm	Concentrated carbo-hydrate source Osmotically less active

FAT								
Lipomul	6.6					Corn oil		Concentrated fat source
MCT oil	7.6					MCT		For malabsorption of long-chain fats
PROTEIN								
SCM-20 Cherry Greatfruit	2.0				Hydrolyzed collagen with limiting AA added			Oral concentrated protein source May be used for protein suppl. or protein-sparing modified fast
Pasteurized egg protein (powder)	3.5 per gm	92.9	6.6	0.49	Powdered egg white		48	Oral concentrated protein source May be used for protein suppl. or protein-sparing modified fast

Table 4. *Classification of Surgical Catabolism**

DEGREE OF NET CATABOLISM	$[N_{obg}]$† GM UREA-N PER DAY	PER CENT INCREASE OF RME OVER BEE
1° Normal	< 5 gm	None
2° Mild	5 to 10 gm	0 to 20
3° Moderate	10 to 15 gm	20 to 50
4° Severe	> 15 gm	> 50

*Classification of patients according to the following: (1) obligate nitrogen loss $[N_{obg}]$ expressed in gm urea-N per 24 hr; (2) energy expenditure expressed as per cent increase of the resting metabolic expenditure over calculated Basal Energy Expenditure.

†No nitrogen intake and 3 days of at least 100 gm carbohydrate.

Data taken from Rutten, P., Blackburn, G. L., Flatt, J. P., et al.: Determination of optimal hyperalimentation infusion rate. J. Surg. Res., *18*:477, 1975. Used with permission.

Given the near constant proportion of nitrogen contribution to caloric expenditure during injury, the metabolic expenditure in excess of the calculated BEE can be estimated from daily urinary urea nitrogen losses.[15] Table 4 provides a classification of surgical catabolism based on the relationship. Most medical illnesses will fall into the first or second degree of catabolism. Net protein utilization (NPU) is at a maximum (72±10 per cent) at intakes of protein and calories recommended above. No further benefit occurs on feeding 2 × BEE as hyperalimentation solutions, because excess intake results in hypermetabolism and diminished NPU.[55] Major burns, however are associated with 4° catabolism in which the energy requirements may exceed 2.5 × BEE.[67]

Consuming the recommended protein intake by depleted adults will produce positive nitrogen balance and restore lean body mass.[50, 55] Nutritional depletion improves the ease with which positive nitrogen balance is achieved while stress antagonizes the utilization of dietary protein. Because 16 per cent of caloric expenditure during injury comes from protein sources, 16 per cent of the calculated calorie needs (1.76 × BEE) should be the optimal protein intake. The remaining calories are provided from nonprotein sources to yield a nitrogen to calorie ratio of 1:150—the best ratio for anabolism. In the nitrogen-accumulation disorders due to renal and hepatic failure where large protein intakes may have detrimental effects, ratios of 1:450 to 1:700 are optimal for nutritional support and physiologic function.

Maintenance diets where 8 per cent of the calories are provided as protein preserve the lean body mass in convalescent patients.[19, 39] This value is approximately half that necessary in stressed patients indicating that the reutilization of body protein during stress is much less effective. A 1:300 nitrogen to calorie ratio is particularly important when "elemental" or chemically defined diets are used because each gram of amino acids beyond this ideal ratio influences osmolality, taste, and ultimately the acceptability of the protein.[19] The source of nonprotein calories, which may be from sugar, starches, dextrin, and medium and long-chain triglycerides also affects osmolality and digestibility and must be kept in mind when devising strategies and formulas for meeting energy requirements.[3, 57]

	FED STATE	NON/FED STATE (Semistarved)
ENTERAL FEEDING	House diet Supplement "DFD"[1]	Clear liquids Fruit juice and gelatin High protein; low CHO "PSMF"[2]
PARENTERAL FEEDING	Hyperalimentation 1. Continuous 2. Cyclic 3. Intralipid	D_5W[3] A_3W[4] Intralipid Ringer's solution

1. Defined formula diet
2. Protein-sparing modified fast
3. 5 per cent dextrose and water
4. Isotonic (3 per cent) amino acids

Figure 2. An approach to the design of nutritional support is to consider two nutritional states (fed and semistarved) and two means of delivery (enteral and parenteral). All available nutritional therapies can be considered in one or more blocks. Enteral modules should always be included and enteral-parenteral therapy is more effective.

The rate and ratio of feeding having been established, the next major consideration is the objectives of treatment—whether "fed" state or "nonfed" (starved) state—and the route of administration—enteral and/or parenteral (Fig. 2). There are unique indications for and advantages with both these routes but a combination is often possible and desirable. Improvement in visceral protein synthesis may occur when classical hyperalimentation is supplemented by enteral feeding of small amounts of protein.[14] Conversely, in the irritable bowel syndrome, pancreatitis, or malabsorption, it may be necessary to supplement enteral feedings by parenteral isotonic amino acids in order to obtain appropriate protein calorie ratios.

ORAL (ENTERAL) FEEDING

If the alimentary tract is functional, it is always the preferred route for nutritional support. The absorption of the nutrients by the portal system with subsequent delivery to the liver has profound effects to support visceral protein synthesis and regulate body metabolism. Figure 2 shows the currently available enteral nutrition products and the feeding situations appropriate for their use. Table 1 contains the composition of common nutritional supplements. In general, these products provide 1 cal per ml when consumed at their recommended concentrations, but they differ widely in their source of protein and calories and the ratio between these two nutrients. Many of the diets exceed the optimal nitrogen to calorie ratio, but can serve as modules which can be supplemented with low protein-high calorie foods acceptable to the patient which would not provide adequate nutrition if given alone.

The carbohydrate composition of the diet is important for two reasons. Many patients requiring nutritional support have lactose intolerance, and

the oligosaccharides are less osmotically active than mono- or disaccharides. The complexity of fat digestion makes it likely to be impaired in many diseases. Thus, the presence of fat beyond the minimal level necessary to prevent essential fatty acid deficiency (1 per cent) is an important consideration in choosing a product. The rationale for using medium-chain triglycerides (MCT) as an alternate energy source relates to their unique metabolism.[57] MCT are digested more rapidly than long-chain triglycerides, not dependent upon micelle formation, rapidly transported across cell membranes, and taken directly into the portal circulation where they are preferentially oxidized by the liver. The taste, osmolality, and viscosity will be important depending upon patient cooperation, bowel irritability, and whether tube feedings will be employed, respectively. Most enteral products are started at half strength at slow feeding rates progressing first to desired feeding rate and then to desired total volume.[4, 20, 60]

Many of the products contain protein of high biologic value. No important clinical significance has been shown in the digestibility or utilization of egg albumin, hydrolysates, or amino acids that have the egg protein profile.[19, 36] However, significantly improved patient taste, acceptance of, and cost differences between whole protein and hydrolysates or amino acids provide a strong recommendation for the use of whole protein except in those few instances where protein maldigestion is likely to be clinically significant.

The A.M.A.'s Council on Food and Nutrition's recent conference on Defined Formula Diets provides a comprehensive review of these relatively new products (see Table 2).[3] Generally known as elemental diets or space food, these products originated from a NASA requirement for a low residue, concentrated food compatible with the conditions in spacecraft. This first generation of products was adapted for use in the medical field without due consideration of the differences in the nutritional status, physical requirements, and activity of astronauts and patients with disease. The constant theme of this conference was the paucity of well controlled studies that would allow proper evaluation of these products. Long-term comprehensive evaluation of the effects, efficacy, and safety in a variety of patients utilizing these products is not now available. For a more detailed discussion of the protein sources, fat content, carbohydrate content, osmolality, effects, gut flora, indications, and methods of utilization the reader is referred to the bibliography of the proceedings of the conference.

One important disadvantage of these products is the fixed compounding making it necessary to carry many products on the hospital "shelf." The concept of "modular" feedings arose out of the necessity to reduce stock to a manageable size. Maintaining basic diets that provide maintenance nutrition using 30 to 35 kcal per kg per day with a nitrogen calorie ratio of 1:300 and an anabolic nutrition product (40 to 45 kcal per kg per day with a nitrogen:calorie ratio of 1:150) appear adequate (for most products). These diets can be supplemented with various single nutrient supplements (modules) consisting of protein, fat, or carbohydrate (Table 3 and Fig. 2). Whether to use the standard defined formula diets or to modify

them would be determined by the assessment of protein utilization by the technique previously described (e.g., nitrogen balance using urinary urea nitrogen excretion).[15]

Because enteral products are relatively expensive when compared to the normal hospital food, it is important that they be used wisely. An equally important consideration however is their cost in relation to total daily hospital cost. By this criterion these products are often cost-effective. A qualified dietitian should monitor the administration of these products to insure that they are acceptable to the patient, are taken in sufficient but not excessive quantity, and that their use is integrated into the medical/nursing plan for the care of the patient. With further education and clinical experience in nutrition, proper use of these beneficial products based on an objective nutritional assessment will be more widespread. Recent development of effective enteric-coated pancreatic enzyme (experimental enzyme, Johnson & Johnson) may diminish the need for predigested diet.[19]

PARENTERAL FEEDING—TOTAL PARENTERAL ALIMENTATION

Recent development of total parenteral nutrition by Dudrick, Wilmore, Vars, Rhoades and co-workers at the University of Pennsylvania[24] has elevated clinical nutrition to a full-time hospital specialty since an experienced team is required to obtain the life-saving results at an acceptable risk and cost/benefit ratio. Parenteral nutrition by necessity is modular because the Maillard reaction precludes compounding amino acids and carbohydrates for long periods prior to use. In addition, Freeman and Stegink report chelation of zinc and copper by sugar amine complexes when protein and carbohydrate are autoclaved together.[30]

Table 5 lists the available or planned products for intravenous use. The observation that infused amino acids are better utilized than protein hydrolysates has led to a substantial shift to amino acids in parenteral feeding.[4] The relative availability of casein, fibrin, and amino acids has contributed to this shift. Two other advantages are the minimal risk of allergy with amino acid infusions and the versatile way in which amino acids can be used therapeutically in different disease states including cancer and renal and liver failure. It is possible that single amino acids or various groups or their ketoanalogues can improve parenteral feeding by a pharmacologic effect.[18, 28, 56, 62]

While good results may occur by using the "hyperalimentation" kits which are commercially available, many patients can benefit from individualization of infusate composition.[45, 55] These products are already provided in separate modules: protein, calories (glucose or fat), minerals, vitamins, and electrolytes which can be used according to the patient's requirements (Table 6 lists the usual additives). Customizing the formulation, adjusting the infusion rate and timing can result in better protein utilization with less alteration in blood chemistries and improvement in organ function. Similarly, control over composition enables the clinical

Table 5. *Concentration of Protein Hydrolysates, Amino Acids, and Various Salts per 100 ml of Commercially Available Products*

	FREAMINE II 8.5 PER CENT (MCGAW)	TRAVASOL 5.5 PER CENT (TRAVENOL)	VEINAMINE 8 PER CENT (CUTTER)	ABBOTT AMINO ACID SOLUTION 3.5 PER CENT	AMINOSOL 5 PER CENT (ABBOTT)	HYPROTIGEN 10 PER CENT (MCGAW) CASEIN HYDROLYSATE 10 GM	CUTTER PROTEIN HYDROLYSATE 5 PER CENT CASEIN HYDROLYSATE 5 GM
ESSENTIAL AMINO ACIDS (in mg)							
L-Isoleucine	590	263	490	252	218	500	240
L-Leucine	770	340	350	329	636	820	415
L-Lysine	870 (as Ac)	318	670	252	400	700	350
L-Methionine	450	318	430	140	100	320	220
L-Phenylalanine	480	340	400	154	100	400	230
L-Threonine	340	230	160	182	232	380	180
L-Tryptophan	130	99	80	56	50	80	50
L-Valine	560	252	250	280	163	600	300
DL-Methionine						130	
DL-Tryptophan						32	

NONESSENTIAL AMINO ACIDS							
L-Alanine	600	1140	*	448			
L-Arginine	310	570	750	343	290		
L-Histidine	240	241	240	105	116		
L-Proline	950	230	110	300			
L-Serine	500			147			
Aminoacetic Acid (Glycine)	1700	1140	3390	448	208		
L-Cysteine HCl	20		*		30		
L-Tyrosine		22	*	31	110		
L-Glutamic Acid			430		30		
L-Aspartic Acid			400		30		
ELECTROLYTES (in mEq)							
Sodium	1	7	4	4	1	5.0	3.9
Chloride		7	5	4		3.6	
Potassium		6	3	1.8	1	3.6	1.8
Magnesium		1	0.6	0.3		0.4	
Acetate		13	5	1.6		*	
Phosphate	2	6	*			5.0	
Calcium			*			1.0	

*Reduced by process

Table 6. *Hyperalimentation Fluid Orders (to Begin on Completion of Previous Orders)*

I. CENTRAL LINE:
A. _____ml hyperalimentation (unless otherwise specified, the solution will be 4.25 per cent FreAmine, 25 per cent glucose) or _____per cent FreAmine, _____ per cent glucose
Additive usually required, please specify:
_____mEq per day NaCl (60 to 80 mEq per day)
_____mEq per day KCl (60 to 100 mEq per day)
_____mEq per day calcium glucepetate (9.0 mEq per day)
_____amp per day magnesium sulfate (8.1 mEq per day)
_____mEq per day potassium phosphate (30 to 45 mEq per day)
_____mg per day folic acid (0.5 to 1.5 mg per wk, Monday only)
_____μg per day B_{12} (50 to 100 mg per wk) Mondays only
_____ml per day Multivit (5 ml per wk) Mondays only
_____mEq per day Na acetate (40 mEq per day)
_____mEq per day K acetate (40 mEq per day)
_____units per liter reg. insulin (10 units per liter)
_____amp per day vit. B and C Tuesday through Sunday
_____Heparin (1000 units per liter)

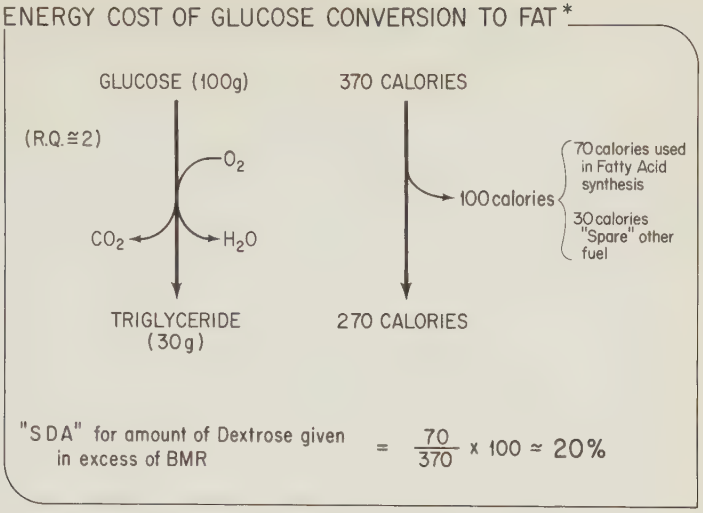
II. RATE OF INFUSION
_____ml per hour

III. LABORATORY TESTS

nutritionist to manage fluid and electrolytes therapy in the presence of renal failure and cardiac failure where restriction is usual as well as in conditions where fluid losses are significant—all without the need for auxiliary intravenous lines.

Some new concepts and developments in hyperalimentation should be considered in more detail because they are not widely reported yet. The consequence of over-feeding with standard hyperalimentation is shown in Figure 3. The specific dynamic action (SDA) of glucose conversion to fat during standard hyperalimentation is 20 per cent. The resulting hypermetabolism during hyperalimentation will result in negative nitrogen balance if excess (1.76 ×BEE) calories are not provided. The hyperinsulinism caused by continuous hyperalimentation stimulates lipogenesis and glycogen deposition which account for the fatty liver and hepatomegaly often associated with long term hyperalimentation. Providing additional calories beyond those required to meet the metabolic requirement further accelerates lipogenesis in the liver with no beneficial effect on the metabolic response to injury.[10]

Cyclic hyperalimentation—the administration of amino acids and hypertonic glucose for only part of the day followed by a period of dextrose-free solution—is effective in circumventing some of the adverse effects of continuous hyperalimentation.[5, 10, 47] The rationale behind cyclic hyperalimentation is that a postabsorptive state develops during the time when no glucose is administered. This period of no dextrose encourages the mobilization of fat and carcass protein previously synthesized to restore and maintain serum albumin levels and promote the return of



*Estimates based on *in vitro* carbon flow of glucose conversion to triglycerides.

Figure 3. The specific dynamic action (SDA) for dextrose given in excess of basal metabolic rate (BMR) is higher than normally considered. *RQ* = respiratory quotient.

liver function to normal. Both these processes do, in fact, occur more rapidly with cyclic hyperalimentation.

Some patients undergoing hyperalimentation have partial function of the gastrointestinal tract and oral intake of small amounts of protein in the dextrose-free period is further effective in sustaining visceral synthesis and organ function. There are several other advantages to cyclic hyperalimentation. Essential fatty acid (EFA) deficiency that often accompanies continuous TPN does not develop during a cyclic regimen, because the patient mobilizes his own stores of linoleic acid present in body fat. Lipolysis occurs readily because insulin levels fall when glucose administration is discontinued. Thus cyclic hyperalimentation mimics normal feeding patterns more closely than continuous hyperalimentation. Those patients in whom essential fatty acid stores are insufficient because of previously poor dietary intakes may require exogenous fat as parenteral Intralipid.[9, 45]

It is possible in many patients to plug the "life-line" and allow freedom from the "life-line" during the day for purposes of exercise and improved sense of well being. In the long-term hospitalized patient, cyclic hyperalimentation provides considerable psychic support.

An in depth discussion of the science of hyperalimentation is beyond the scope of this section: the reader is referred to the many current books on the subject.[4, 26, 66, 68] Briefly, it is important to maintain electrolyte, acid-base, and metabolic balance. Regulation of blood urea nitrogen and glucose, preservation of near normal liver function tests, and avoidance of fatty liver, hepatomegaly, and impaired secretory protein synthesis are major parameters (see Table 6). Monitoring and providing co-factors of

Table 7. *Daily Vitamin Requirements*

	RDA		PARENTERAL	
	Adult	Child (1–10 yrs)	Adult	Child
Ascorbic acid	45	40	100 mg	80 mg
Thiamine	1.0–1.5	0.7–1.2	3 mg	1.2 mg
Riboflavin	1.1–1.8	0.8–1.2	3.6 mg	1.4 mg
Niacin	12–20	9–16	40 mg	17 mg
B_6	1.6–2.0	0.6–1.2	4 mg	1.0 mg
Pantothenic acid	5–10		15 mg	5.0 mg
Folacin	400	100–300	40 mg	140 mg
B_{12}	3	1–2	5 mg	1.0 mg
A	4000–5000	2000–3000	3300 IU	2300 IU
D	400	400	200 IU	400 IU
E	12–15		10 IU	7 IU
K_1	2	7–10		0.2
Biotin	150–300		60	20.0

phosphate, magnesium, iron, copper, zinc, and linoleic acid are also essential (Tables 7 and 8). Nitrogen balance is the single most important indicator of the effectiveness of hyperalimentation, since protein metabolism is easily impaired and the most important nutrient for recovery.

Non-Fed Parenteral Feeding

Management of patients to optimize nutrition in the starved state has been relatively ignored. Most physicians have been counseled that it is not worthwhile to provide nutritional support during short periods of starvation, although the adverse effects of short term nutritional depletion are well documented.[15] In the well nourished, injured individual this is justified because the normal response to starvation plus injury precludes effective incorporation of exogenous nutrients.[49, 50]

Many patients, however, are in poor nutritional condition and the period of poor utilization of exogenous nutrients does not last as long as

Table 8. *Daily Mineral Requirements (Parenteral Use)*

Sodium	60–80 mEq per day
Potassium	80–120 mEq per day
Magnesium	8–16 mEq per day
Calcium	9–18 mEq per day
Phosphorus (H_2PO_4)	30–45 mEq per day
Iron	1 mg per day
Zinc	10 mg per day
Manganese	5 mg per day
Copper	2 mg per day
Chromium	.2 mg per day
Cobalt	.05 mg per day
Iodine	.5 mg per day*

*The trace minerals may be put in a 5 ml vial and given orally.

the classic catabolic phase of injury.[49] Although net protein catabolism occurs for several days to weeks after injury, the ability to reverse this trend improves daily, justifying early attention.[15, 17] The failure to minimize the ongoing losses of body cell mass, particularly in nutritionally depleted patients, affects the character of recovery as well as morbidity and mortality.[7, 12]

A major breakthrough in the understanding of the metabolism of starvation came with the demonstration that ketones are a major fuel satisfying brain energy requirements and thus overall energy requirements.[21] This implied that the body could spare its own protein even in the starved state and accounted for the observation that in late fasting, there is reduction in glucose requirements and decreased rates of gluconeogenesis and amino acid oxidation.[49]

Blackburn and Flatt developed a first order approximation of the interrelationship of protein, fat, and carbohydrate in the metabolic fuel cycle. This model provides the basis for understanding the protein-calorie requirements during the starvation.[17, 29] In the starved state substantial amounts of protein can be spared by the parenteral infusion of amino acids or oral intake of protein. The infusions maintain protein synthesis particularly in the viscera, while allowing body fat stores to be mobilized.[17, 31, 43]

This concept runs counter to the later interpretation of Gamble's classic studies on life raft rations.[32] In human volunteers without stress, decreased nitrogen losses, ketosis, and ketonuria were noted when they were fed 100 grams of glucose. Others have inferred from these observations that the most effective protein-sparing during the non-fed or starved state is the use of 2 liters of 5 per cent dextrose and water.

However, an increasing body of evidence indicates that during the acute phase of injury glucose is no more protein-sparing than starvation alone.[33] The sympathetic mediated response to injury increases the mobilization of peripheral stores of fat and improves the utilization of the mobilized amino acids and maintenance of lean body mass.[17] The administration of glucose elevates insulin levels, effectively shunting amino acids to the periphery and thereby hampering efforts to support visceral protein synthesis.[15, 26]

The efficiency of using carbohydrates in small amounts either orally or intravenously is now subject to question.[25, 49, 52] A considerable body of research suggests that the use of 1.0 to 1.5 gm protein per kg ideal body weight (IBW) per day with appropriate co-factors of vitamins, minerals, fluids, and electrolytes represents the best management of the starved state.[13, 15]

ORAL PROTEIN SPARING

The reasoning behind oral protein sparing is the same as that for intravenous protein sparing; its benefit and importance have been demonstrated by improvements in serum albumin and transferrin levels, and immunocompetence.[8, 14] Oral protein given at the rate of 1.5 gm

protein per kg ideal body weight per day gives results similar to intravenous amino acids.[14] TPN may be indicated if patients after 2 or 3 weeks of oral protein sparing continue to have a significantly negative nitrogen balance or if their nutritional status were initially poor.

When starting a patient on clear liquids it is desirable to use oral protein which the gastrointestinal tract, liver, and other key viscera selectively utilize to complement the protein-sparing effect of intravenous amino acids. Besides the usual sources of animal protein including meat, fish, and fowl, tryptophan-enriched collagen and soy protein isolate can be incorporated into clear liquid diets as a substitution for presently used carbohydrate-based products. The intake of 30 gm of protein incorporated in 60 ml fluid volume is easily tolerated and can have a salubrious effect on protein metabolism (cf. SCM-20, Table 3). The combination of such oral protein-sparing therapy with parenteral hyperalimentation is another important adjunctive therapy. Whenever possible, nutritional support plans should provide some oral protein intake due to its beneficial effect on liver protein metabolism. The levels used can safely approach the recommended daily allowance of 0.8 gm protein per kg per day to anabolic requirements of 1.5 gm per kg per day.[50]

SPECIAL DISEASE CONSIDERATIONS

Renal Failure

The treatment of renal failure was revolutionized by Giordano and Giavonetti in 1963 with the introduction of a low protein diet containing protein of high biologic value and adequate-to-excess calories.[35] The diet was based on the pioneering work of Rose et al.[54] in the 1950's which had established the human requirements for essential amino acids and nonessential nitrogen. Not only does the Giavonetti diet provide adequate essential amino acids, but experience has also shown that endogenous urea nitrogen can be recycled for protein anabolism.[62] The benefit of this diet in the treatment of chronic renal failure has been demonstrated by improvement in the hypoplastic anemia, lowering of the blood urea, achievement of nitrogen balance, and disappearance or improvement of uremic symptoms, such as anorexia, vomiting, muscle twitching, and decreased mentation. The effectiveness of this diet depends upon (1) a high calorie to nitrogen ratio (C:N), (2) the number of calories delivered expressed in terms of the basal energy expenditure, and (3) provision of adequate essential amino acids.[18, 55] While originally developed as an oral diet, for chronic renal failure it has been adapted to intravenous use and acute renal impairment. Acute renal failure due to tubular necrosis frequently occurs in severely traumatized patients or after major surgery when the systemic catabolic response to injury is dominant. Such patients are often unable to use their gastrointestinal tracts for ingestion of nutrients; intravenous feeding can thus support nutrition while recovery from various disease states and associated renal failure occurs.

It is important to emphasize that this therapy is supportive and not a replacement for hemodialysis or peritoneal dialysis in most cases. Abel, Abbott, and Fischer recently concluded extensive trials using essential amino acids in hypertonic glucose that confirmed the beneficial effects of renal failure hyperalimentation as a support therapy.[1, 2, 26] In addition to improving wound healing, minimizing the catabolism of tissue proteins, and reducing the frequency of dialysis,[1] the metabolic benefits include normalization of serum protein, phosphate, and magnesium levels.

There are, however, several unanswered questions in the nutritional management of renal failure. Clinically, solutions containing both essential and nonessential amino acids in crossover studies with essential amino acids alone have not produced substantially different results.[18] Several investigators have demonstrated the semiessential nature of histidine,[6] and improved utilization of protein has also resulted with the provision of arginine and other presumably nonessential amino acids.[6] Thus it would appear that provision of the optimal number of calories to meet the metabolic expenditure along with sufficient protein for optimal protein synthesis and turnover are more important than the amino acid profile. Clinically, an intake of 20 to 30 gm of protein per day at a nitrogen calorie ratio ranging from 1:450 to 1:700 allows for the best protein utilization. Defined formula oral diets containing essential amino acids or their ketoanalogues are also a promising variant in the nutritional support of the patient with chronic renal failure.[12]

Liver Failure

The failing liver is characterized by the decreased ability to metabolize certain amino acids. The recent understanding of the unique metabolism of the branched-chain amino acids[51] and aromatic amino acids[28] has suggested that they represent the most critically regulated amino acids in circulation. For example, tryptophan "detoxification" is primarily dependent upon liver function. Therefore, it is not surprising that the level of tryptophan is elevated together with the other aromatic amino acids during liver failure. Branched chain amino acids, on the other hand, are not significantly metabolized by the liver and become depleted during limited protein intakes. These amino acids are all precursors for brain neurotransmitters with those derived from aromatic amino acids having a depressant effect on cerebral function. Branched-chain and aromatic amino acids reversibly compete for transfer across the blood-brain barrier and substrate availability is the limiting step in neurotransmitter production. These observations form the basis for development of a liver failure diet formula to normalize amino acid levels that will be beneficial in future generations of products.[18]

The nonprotein calories of liver failure are also important and have given rise to products that are alcohol-free and utilize medium-chain triglycerides and a judicious distribution of sugars, starches, and dextrins. The therapeutic goal, whatever the energy source, is the provision of calories sufficient to meet the energy requirement without causing the extra work of lipogenesis, gluconeogenesis, and ureagenesis by the failing liver.

PEDIATRIC PROTEIN AND CALORIE REQUIREMENTS

The discussion in this section provides only general guidelines to pediatric nutritional therapy. Complications with initial therapy or metabolic disorders are extensively discussed in the references;[39, 40, 68] it is essential that those physicians faced with difficult nutrition support problems in children use these primary sources.

The calorie requirement for newborn infants represents the highest concentration (cal per kg) seen in man. The average basal metabolic requirement is assumed to be 55 cal per kg per day; spontaneous activities requires 25 cal per kg per day, and weight gain of 8 gm per kg per day requires 5 cal per gm. Thus the total desired oral intake would be 120 cal per kg per day. Total parenteral feeding can produce weight gain and survival at levels less than 120 cal per kg per day. It is yet to be established if any of these areas—basal metabolism, activity, or weight gain—is compromised by such feedings. Winters* has observed that maintenance of thermoneutrality will allow growth in the first few days in the neonate by as few as 60 cal per kg per day.

Once the infant's weight reaches 10 to 20 kg, caloric requirements drop to 50 cal per kg per day and then to a resting metabolic rate requirement of 25 cal per kg per day once weight is in excess of 20 kg. These levels are similar to those in adults. Similarly when disease is associated with hypermetabolism from fever, sepsis, burns, and other major trauma the desired caloric intake is 35 to 40 cal per kg per day.

The protein requirement for growth in infants is usually 3 to 4 gm per kg per day. 2.5 gm per kg per day is adequate parenteral feeding to produce positive nitrogen balance. This level will decline to 2 gm per kg per day in 10 to 20 kg infants and to the levels used in adults (1–1.5 gm per kg per day) when infant weight exceeds 20 kg.

Peripheral total parenteral feeding requires the use of 10 per cent Intralipid (40 ml per kg per 24 hr) with a mixture of 10 per cent dextrose and 3 per cent FreAmine (85 ml per kg per hr) totaling 125 ml per kg per hr. This therapy delivers 2.5 gm of amino acid per kg per day and 100 cal per kg per day. The peripheral line requires two infusion pumps and a Millipore filter with the Intralipid infusion entering below the filter. Infusion, via a 21 to 23 gauge scalp vein needle, may be given for many weeks in adequate amounts without requiring cutdown in experienced hands.[4, 68]

Usually partial (supplemental) oral feedings can make up for any energy deficit. Indeed parenteral and enteral feeding combined is desirable in order to make up for any weight loss or temporary gastrointestinal setbacks during the important early growing phase of the infant.

Central venous hyperalimentation also provides an opportunity to deliver high caloric intake with less fluid intake but threatens serious complications.

Carbohydrate can serve as the total source of calories with this technique at an infusion rate of 20 mg glucose per kg per minute. Since the rate of disappearance of glucose in the newborn is 3.5 per cent per minute, glucose homeostasis is maintained by this therapy.

*R. W. Winters and W. Heird, personal communication.

The central venous technique requires a full-time physician, a nurse, and a pharmacist to direct intravenous nutritional support with an acceptable complication rate. Complications of central venous total parenteral feeding in children are similar to those in adults. In addition, amino acid intolerance, hyperaminoacidemia, and septic complications are more frequently seen. These conditions require an experienced team to obtain a proper risk/benefit ratio from this important therapy.

Oral Feedings

Consideration of oral diets is dependent upon knowledge of intestinal absorption and transport. Carbohydrate and protein are absorbed in the proximal small intestine after being digested to simple sugars and amino acids. Fat is absorbed throughout the small bowel depending upon lipase activity and bile salt for hydrolysis and absorption. Various difficulties with absorption after digestion have given rise to numerous special infant diets which are contained in Table 9. Most of these diets contain predigested, carbohydrate sources and are pH regulated in order to facilitate their absorption.

It is important to realize that infants have unique flavor tolerances and therefore unflavored products such as Vivonex HN and Progestimal are well tolerated and effective feedings for many infants.

For many diseases predigested protein and/or carbohydrate are not essential. A lower osmolality can be obtained with the use of whole protein, dextrins, and hydrolyzed corn starch or its equivalent, together with medium-chain triglycerides.

For many patients who have undergone prolonged bowel rest or significant bowel resection, considerable time is necessary to allow for the adaptation and restoration of intestinal villi. Gastric hypersecretion and bacterial overgrowth are also important factors to be considered in nutritional support during malabsorption.

SUMMARY

Nutritional therapy is influenced both by disease and nutritional status. In addition, the degree of protein depletion in large part dictates the urgency of aggressive nutritional therapy. The presence of hypermetabolism where the hormonal substrate response is distinctly antagonistic to replacement therapy precludes effective repair of nutritional depletion. Sepsis further antagonizes efforts at nutritional support. For these reasons no elective or semielective procedure that carries a risk of prolonged stress, hypermetabolism, and sepsis should be performed until adequate nutritional status has been obtained.

Enteral feeding programs are to be preferred due to their risk-benefit and cost-benefit ratios. However, impaired digestive function related to disease often limits their use and reliance on parenteral nutrition becomes necessary. While each patient has unique needs and responses, a systematic approach based on objective measurements will most often result in effective nutritional therapy. The accomplished therapist will

Table 9. *Composition and Indications for Use of Pediatric Formulas*

PEDIATRIC FORMULAS	CAL PER ML	MOSM PER L	PER CENT CAL PROTEIN	PER CENT CAL FAT	PER CENT CAL CARBO-DRATE	N:CAL	PROTEIN SOURCE	CARBO-HYDRATE SOURCE	FAT SOURCE	meq NA PER L	FUNCTIONS
Enfamil	0.7	262	9	50	42	1:256	Powdered milk	Lactose	Corn oil	11.5	House feeding, milk fat intolerance, like breast milk
Enfamil with Fe						1:256		Corn syrup	Coconut oil	11	
Similac	0.7	156	10	48	42	1:243				11	With Fe for anemic mother, low birth wt., blood loss
Similac with Fe						1:243				11	
Breast Milk	0.7	116	8	50	42	1:311	60% lactalb. 40% casein	Lactose	Human milk fat	7	
Cow's Milk	0.7	307	20	54	29	1:102	Casein	Lactose	Butter fat	22	
Pregestimil	0.7	539	13	38	52	1:173	Casein hydrolysate	Glucose Dextrose	MCT corn oil	17	Dissac. def., steatorrhea, intest. resection, chronic diarrhea, food allergy, cystic fibrosis, pancreas

Nutramigen	0.7	416	13	35	51	1:165	Protein hydrolysate	Sucrose Arrowroot Starch	Corn oil	13	Colic, protein (milk in vomiting), diarrhea
Lofanalac	0.7	393	13	35	52	1:168	Casein hydrolysate	Sucrose Dextrose Maltose	Corn oil	20	PKU Infant formula, child's milk
Premature	0.8	351	14	41	45	1:155	Casein hydrolysate	Sucrose Lactose	Corn oil	20	Premature, high protein high cal. 120 cal/kg 4 gm prot/Kg
Portagen	0.7	203	14	42	44	1:155	Na caseinate lactalb.	Corn syrup	MCT oil Corn oil	17	Fat malabsorb., MCT low bile, low pancreatic function. Low intestine surface
SMA 26	0.7	236	9	42	43	1:255	Pwd. sk. milk Demineralized whey	Lactose	Corn, soy, coconut oils	6	Low Na^+

apply the "modular" approach using the wide variety of products and techniques now available.

Ignoring the support of protein synthesis and the preservation of lean body mass can no longer be considered good patient care even in the management of the semistarved state. There is no longer any justification for allowing nosocomial malnutrition to alter the morbidity and mortality of disease.

With proper skills in the techniques of protein-calorie therapy and the availability of adequate techniques for nutritional assessment, the science of nutritional therapy now affords the opportunity to provide optimal care for the injured hospitalized patient.

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